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PAUL EHRLICH MEMORIAL ISSUE
1854—1954

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PAUL EHRLICH—AS MAN AND SCIENTIST — *Selman A. Waksman*

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OPHTHALMOLOGY

THE EFFECT OF TRIPELENNAMINE HYDROCHLORIDE ON VISUAL ACUITY, COLOR PERCEPTION AND STEREOPTIC PERCEPTION AS EVALUATED BY THE ORTHO-RATER — *Austin H. Kutscher, Neal W. Chilton, Stanley L. Lane and Eleanor E. Koepchen*

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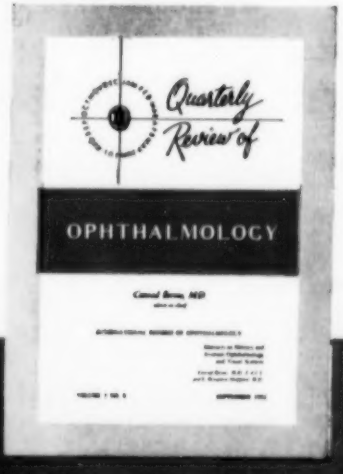

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1. Boland, E. W.: Ann. Rheum. Dis. 12:125, 1953.
2. Boland, E. W., and Headley, N. E.: J.A.M.A. 148:981, 1952.

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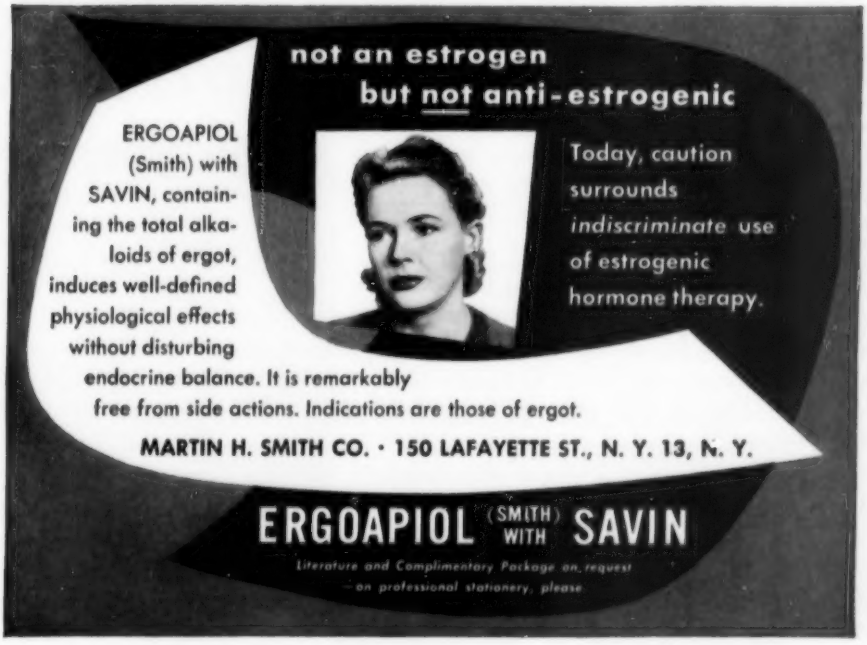
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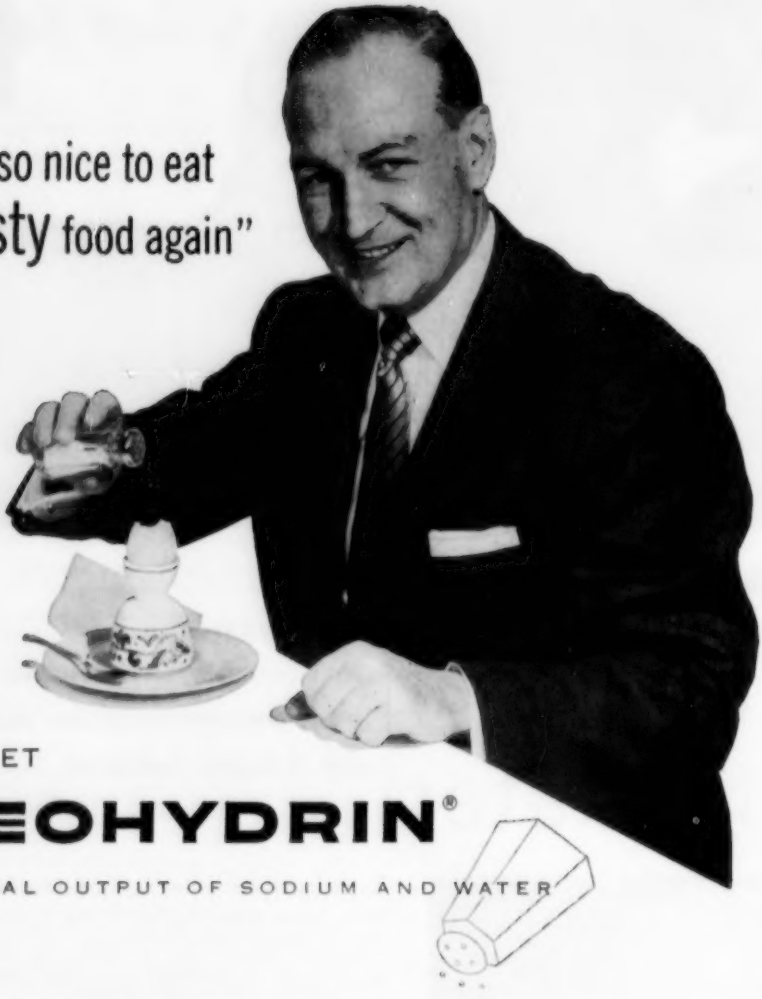

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The Development of Bacterial Chemotherapy*

E. B. Chain, Ph.D., F.R.S.

PROFESSOR OF BIOCHEMISTRY, SCIENTIFIC DIRECTOR, INTERNATIONAL RESEARCH CENTRE FOR CHEMICAL MICROBIOLOGY, ISTITUTO SUPERIORE DI SANITÀ, ROME

HOMAGE TO PAUL EHRLICH

We are commemorating today the one hundredth anniversary of the birthday of Paul Ehrlich, the founder of modern antimicrobial chemotherapy. The significance of this date in the history of therapeutic medicine can hardly be overemphasized, for mankind owes to Paul Ehrlich's pioneering work and its vast influence on research developments in the field of chemotherapy—an influence extending far beyond his own life span—some of the greatest triumphs of medicine over infectious diseases.

Those of us, who are actively engaged in research on chemotherapeutic problems, are still today very conscious of this influence which makes itself felt in our daily work, and, therefore, the centenary of Paul Ehrlich's birthday is for us an event of particular importance which touches us personally.

To be honored on such notable an occasion by the award of the Paul Ehrlich prize and the invitation to give the main commemorative lecture is a distinction and a privilege which I greatly appreciate.

Antimicrobial chemotherapy, in the sense conceived by Ehrlich, is a method of treatment of microbial infections in which the invading pathogens are killed inside the body by means of antimicrobial substances of relatively simple chemical constitution which are of sufficiently low toxicity not to harm the host organism.

The attempt of Ehrlich to incorporate the metal arsenic—whose antispirochetal action was known since the Middle Ages—in an organic compound in a form in which it would retain its antispirochetal action, yet sufficiently nontoxic to be of

* This is the address delivered at The Centennial Commemoration Ceremony held in Frankfurt on March 14–16, 1954, on the occasion of presenting to Ernst Boris Chain (Nobel Prize laureate for Physiology and Medicine in 1945) the Paul Ehrlich and Ludwig Darmstaedter Prize, 1954.

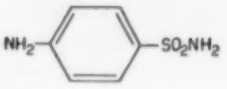
practical use as a drug, culminated in the discovery of the famous compound 606, Salvarsan—the 606th compound which was tested and which proved successful in the treatment of syphilis. This work is too well known to be further commented upon on this occasion.

Another important line of attack by Ehrlich on the problems of microbial chemotherapy emanated from his histologic studies. As is well known—and again, this needs no elaboration here—Ehrlich made fundamental contributions to the progress of histology with the discovery of differential staining.

He discovered that many of the aniline dyes which he used for his histologic studies had strong antibacterial activity, and this led him to hope that in the same way as there existed dyes which specially stained certain cells or parts of cells, while leaving others unaffected, so one day an antibacterial dye would be discovered which exerted a specific toxic effect on the microbial cell, only without affecting the animal cell.

There can be no doubt that the whole of Paul Ehrlich's work on chemotherapy was closely linked to and much stimulated by the prodigious development of the science of organic chemistry in Germany at that time and was greatly facilitated by the concomitant extraordinary expansion of the German dyestuffs industry.

SULPHANILAMIDE



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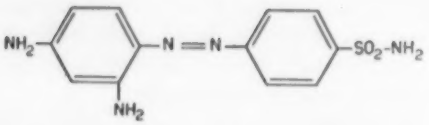


Figure 1.

A large number of aniline dyes made available to Ehrlich were tested by him for chemotherapeutic activity in bacterial infections, but the results were disappointing, for all of them proved too toxic for clinical use. However, this line of investigation was pursued after Ehrlich's death, and led to the discovery in 1935 by Domagk that the aniline azodye prontosil (1) was an effective chemotherapeutic agent against streptococcal infections. This discovery was a most important milestone in the development of chemotherapy, for it was shown for the first time that antibacterial chemotherapy was a practical possibility. However, it was illustrated a few months after Domagk's discovery by a group of workers, Tréfouel, Tréfouel, Bovet, and Nitti, at the Institut Pasteur in Paris, that contrary to Ehrlich's concepts the chemotherapeutic effectiveness of prontosil was not due to its dye nature, but resided in

the noncolored sulfanilamide moiety of the prontosil molecule.(2) Sulfanilamide is a very simple chemical substance and many thousands of analogues were synthesized of which a number had chemotherapeutic power against a considerable range of bacterial infections.

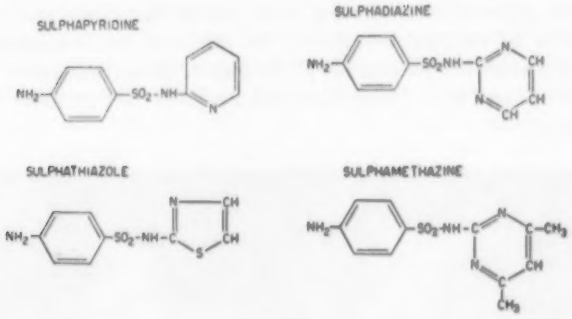


FIGURE 2.

Today we are in a position to combat effectively the majority of the most serious bacterial infections, a situation which probably far surpasses Paul Ehrlich's most optimistic expectations. This remarkable achievement is due to two main independent lines of development. One of these, the development of the sulfonamides, a direct outcome of the ideas advanced by Paul Ehrlich, I have just mentioned. The elucidation of the mode of action of this group of substances by Woods, in conjunction with the very substantial general progress in biochemistry, has opened up new lines of approach to chemotherapy with great potentialities.

The other major development was initiated by the introduction into medicine of the antibiotics, and it is with this subject that my lecture is mainly concerned.

THE ERA OF ANTIBIOTICS: HISTORICAL

Intensive research on antibiotics began in 1940, when Florey, myself, and my colleagues at Oxford University announced that penicillin, a metabolic product of *Penicillium chrysogenum*, whose existence had been observed eleven years previously by the London bacteriologist, Alexander Fleming, possessed remarkable curative properties in experimental animal infections. From that time on the development of the literature on the antibiotics has shown the same logarithmic curve that is characteristic of bacterial growth; it is difficult even for the specialist in this field to follow all the publications whose contents now amount to many thousands of articles.

In this short lecture I cannot hope to cover adequately the whole field of antibiotics. I shall limit myself to a discussion of some of the chemical and biologic results of more general importance.

I should like to begin with a brief historical introduction dealing with the events that led to the discovery of the chemotherapeutic properties of penicillin.

The phenomenon that certain microorganisms are capable of inhibiting the growth of other microorganisms is called "microbial antagonism" and was first described by Pasteur and his co-worker Joubert in 1877. They observed that the growth of *Bacillus anthracis* was inhibited by a nonpathogenic unidentified bacillus which they had isolated from the air. The practical possibilities of this phenomenon for therapeutic purposes became clear to them at once, and, in fact, they were able to inhibit the development of anthrax in rabbits, by injecting the antagonistic air-borne bacillus together with the pathogenic *B. anthracis*. As a consequence of the results obtained, they declared that "these facts perhaps justify the greatest optimism with regard to therapeutics."

FIGURE 3.

Following the observations of Joubert and Pasteur, many examples of various types of microorganisms, such as bacteria, moulds, and yeasts, have been reported capable of inhibiting the growth of other microorganisms. In some cases it was demonstrated that the antagonistic action of one microbial species upon another was due to the production of metabolic antibacterial products on the part of the antagonistic species. These microbial antibacterial products are now known by the name of antibiotics, a term introduced by Waksman. The idea of using these antibiotics in therapeutic medicine is not new. Many and sustained attempts in this direction have been made since 1899. Figure 3 shows a photograph taken from an article published by Emmerich in 1907 in the *Münchener Medizinische Wochenschrift*, in which he illustrates the use of pyocyanase, a mixture of antibiotics produced from *P. pyocyanea*, in the treatment of diphtheria; the antibiotic is sprayed locally in the throat of a child by means of an atomizer.

Clinical use of this mixture of antibiotics continued for many years, but without satisfactory results. The antibiotic preparations used did not differ essentially from

the numerous synthetic antiseptics then available, e.g., mercuric chloride, iodine, formalin, soaps, acridines, etc., all of which were far too toxic to be used as chemotherapeutic agents.

This was the situation in the antibiotic field at the end of 1938.

In this year, I had occasion to review the older literature on antibacterial substances produced by microorganisms. It appeared that a very large number of such substances had been described, but that very little was known concerning their chemical or pharmacologic properties. Therefore, in the hope of finding new kinds of antibacterial substances and, thus, of opening new approaches for the organic chemist and biochemist which could lead to development of new antibacterial preparations, Professor (now Sir Howard) Florey and I at the School of Pathology in Oxford decided to undertake a systematic study of their chemical and pharmacologic properties.

Among the numerous examples of microbial antagonism mentioned in the literature, one that particularly attracted our interest had been reported by Fleming in 1929. He had observed that one of the agar plates on which he had been growing staphylococci, had been accidentally contaminated by a mould belonging to a genus *Penicillium*, and that the colonies of staphylococci near the contaminating mould had begun to disappear (fig. 4). This phenomenon of antagonism between a mould and staphylococci was so striking that it called for further investigation. Fleming subcultured the mould and allowed it to grow on the surface of a culture fluid of the type normally used in bacteriologic work. He found that the culture fluid, after the mould had covered its surface, had acquired a strong power to inhibit the growth not only of staphylococci, but of many other pathogenic gram-positive bacteria, while it had no influence on gram-negative bacteria with the exception of the gonococcus and meningococcus. It was evident that the mould had produced an active antibacterial principle, but since at that time the nature of this principle was unknown, nor was it known whether it consisted of one single substance or a mixture of substances, Fleming gave the name penicillin not to a particular antibacterial substance, but to the whole culture filtrate of the mould which possessed bacterial growth-inhibiting properties. The mould was subsequently identified by the American mycologist Thom as *Penicillium notatum*. Fleming had stated that penicillin could be used for local treatment of infected wounds, without showing greater toxic effects than ordinary culture broth; but many synthetic antiseptics could be (and in fact were) used for the same purpose. His observation therefore

FIGURE 4.

attracted no particular interest. Nevertheless, Fleming had shown that penicillin differed from the then-known antiseptics in one important aspect, namely that it was not toxic to the leukocytes of the blood. It will be remembered that at that time, six years before the introduction of prontosil by Domagk and the sulfonamides by Tréfouel, Tréfouel, Bovet, and Nitti, the attitude of the majority of bacteriologists to bacterial chemotherapy was an entirely negative one, and this explains why Fleming's observation had aroused so little interest.

The crucial test to discover whether penicillin could be used internally as a chemotherapeutic agent against bacterial infections, a test which would have placed penicillin in a category fundamentally different from all other antibacterial substances then known, was not performed. In any case it is doubtful whether this test could have been carried out at that time with the crude culture fluid, without having available the antibacterial principle isolated from the culture fluid in an at least partly purified form. A substance, in order to be classified as a chemotherapeutic agent, must satisfy a number of very rigorous conditions. Among these the two most important are that (1) its antibacterial properties must be retained in the tissues, and (2) it must not exert toxic effects in antibacterial concentrations not only after a single injection, but also after repeated injections over prolonged periods of time.

Only a detailed pharmacologic study can demonstrate whether an antibacterial substance possesses these properties, and in the case of an antibiotic it is clearly impossible to carry out such research on the crude culture fluid upon which the organism producing the antibiotic has been grown, without having first concentrated and purified the metabolic antibacterial product.

The isolation of the antibacterial principle of *Penicillium notatum*, even in a partially purified state, was not a straightforward process. It was attempted in 1932, three years after Fleming's discovery, by Professor Raistrick and his co-workers at London University, but with little success. The active principle was described as very unstable, and it was found that it was destroyed under the conditions in which isolation from the culture fluid was attempted. Following these results, work designed to isolate the antibacterial principle of *P. notatum* was no longer pursued in Raistrick's laboratory. The fact that Professor Raistrick, a pioneer in the field of metabolic mould products, who had isolated hundreds of these substances and elucidated their chemical structure, did not persevere with his work, must undoubtedly be attributed to the generally negative attitude of the bacteriologists of the day to the possibilities of chemotherapy. This attitude was so deep-rooted that no one at that time even vaguely suspected that a substance like penicillin could possess properties fundamentally different from those of any other then-known antibacterial substances, which would allow its use for the clinical treatment of systemic bacterial infections.

THE DISCOVERY OF THE CHEMOTHERAPEUTIC ACTION OF PENICILLIN

To begin our systematic study, Florey and I selected some of the numerous examples of antibiotics reported in the literature, among them Fleming's penicillin, upon which our attention was ultimately concentrated. The reasons for the selection

of penicillin were both biochemical and biologic in nature. Penicillin was one of the few antibiotics upon which at least a few chemical observations, incomplete though they were, had been made, and the conditions for its production seemed to be relatively easily reproducible. The instability of penicillin reported in Raistrick's work, which was the cause of the difficulties encountered in its isolation, particularly attracted my attention as a biochemist, because it seemed to indicate that the active principle had an unusual chemical structure that was not present in any of the known antibacterial substances. The fact that the principle was active against the staphylococcus, for which at that time no other remedy was known, particularly attracted Florey's interest as a pathologist. Work on penicillin was begun about one year before the war; it was thus not stimulated, as is so often stated, by wartime demands for new and effective methods of treating infected wounds. It is perhaps important to emphasize that the decision to reinvestigate the properties of penicillin was *not* motivated by the hope of developing the clinical application of an antibacterial substance which had been shown to have great practical possibilities, but for some incomprehensible reasons had been overlooked for nine years. The published work on penicillin did not contain any indication that could have justified the hope that penicillin would have any practical value. On the contrary, the instability of the antibacterial principle already referred to could only be considered a disadvantage, as regards its use in practical medicine. The investigation was undertaken essentially as a biochemical problem, with the aim of establishing the chemical nature of a natural, very unstable, antibacterial product active against the staphylococcus.

The strain of *Penicillium notatum* which produced penicillin, and with which the Oxford studies were begun, was a descendant of Fleming's original strain, that happened to be available at the School of Pathology in Oxford.

The extraction from the culture fluid of the antibacterial principle produced from *P. notatum*, in a form which was very impure but relatively stable, and suitable for animal experiments, was a relatively simple matter. My colleague Heatley and I obtained it after establishing the conditions for its production and some of its most important chemical properties. The name penicillin, which Fleming had given to the antibacterial culture fluid, was retained by us for the active antibacterial principle contained therein. Subsequently it was shown that this active principle consisted not of one single substance, but of a mixture of different substances, although the chemical structure of these was very similar.

The first preparations of penicillin which were obtained, impure though they were, had a powerful inhibitory action on the staphylococcus, being effective at a dilution of 1:500,000; thus they were about ten times more active than the sulfonamides under optimum conditions. The injection of these preparations into animals showed immediately that they had a remarkably low toxicity and that they retained their antibacterial action in the animal organism. Thus, it appeared that penicillin possessed the two important properties referred to above which are required of a chemotherapeutic agent.

In fact, the first experiments on mice infected with streptococci, even though they were carried out on a very small scale, clearly demonstrated that penicillin was capable of influencing favorably the course of bacterial infections.

Further experiments on animals carried out in collaboration with other members of the Department (A. Gardner, J. Orr-Ewing, M. A. Jennings, and A. G. Sanders) showed that penicillin was indeed a chemotherapeutic agent which would effectively cure severe infections with staphylococci, pneumococci, and anaerobic organisms such as *Clostridium welchii* and *Clostridium cedematiens*. It was almost incredibly good luck that the very impure preparations of penicillin which were used for these experiments, and which demonstrated the chemotherapeutic action of penicillin, had such a very low toxicity. We know now that despite their strong antibacterial activity, these preparations contained less than 1 per cent of penicillin; the rest of the material consisted of a mixture of many different substances, each of which might have been sufficiently toxic to mask the nontoxicity of penicillin. The first toxicity tests on man, which followed the animal experiments, showed in fact that penicillin preparations used so effectively in the animal experiments were too toxic for clinical use, and therefore further purification became necessary. Although the first extraction of penicillin from the culture fluid was a relatively simple operation, the further purification proved to be unusually difficult and gave a great deal of trouble to many chemists in Great Britain and in the United States. This was due to the fact that penicillin, in confirmation of the early results of Raistrick and his co-workers, was in fact a very unstable substance, although, fortunately, completely stable in the conditions in which it has to work in the animal organism.

Abraham and myself, after an extensive study of the chemical properties of penicillin, succeeded in obtaining a purer preparation which was shown to be sufficiently nontoxic for clinical use. The first clinical trials with this preparation confirmed the animal experiments and demonstrated that penicillin was a most effective chemotherapeutic agent in many of the severest bacterial infections in man.

With the discovery of the chemotherapeutic action of penicillin by the Oxford workers (their work was published in two articles in *Lancet*; one in 1940 on the results of the animal experiments and the second in 1941 on the first clinical trials) a new era in bacterial chemotherapy began—the era of antibiotics, which has not yet reached the end of its development.

ANTIBACTERIAL RANGE AND CLINICAL USE OF PENICILLIN

Penicillin is the most active and the least toxic antibacterial substance known. It is active against gram-positive bacteria and against some gram-negative organisms such as the meningococcus and the gonococcus. It is also very active against the spirochete causing syphilis. For about eight years, only the pure crystalline salts of penicillin have been used clinically. Pure penicillin has an activity about 200 times as great as that of the sulfonamides, being effective in a dilution of 1:100,000,000; it is practically nontoxic even in high doses. In fact, pharmacologically it is almost completely inert, except for the fact that it is responsible for allergic symptoms in 5 per cent of the patients treated. Thus, it has properties far superior to those of the sulfonamides and, in its combination of an extremely high antibacterial activity with almost complete lack of toxicity, it has remained unique among all the chemotherapeutic substances known up to the present day. Clinically it is effective in all

the diseases caused by bacteria which are penicillin-sensitive. Particularly remarkable results have been obtained in severe cases of infections with staphylococci, streptococci, pneumococci, gonococci, and meningococci. Administered in high doses, it has been used with success in the treatment of bacterial endocarditis, a disease whose mortality rate was 100 per cent before the introduction of penicillin. Penicillin, unlike the sulfonamides, keeps its full antibacterial activity in the presence of pus and of breakdown products of the tissues, and its antibacterial activity is not influenced by the number of bacteria present. It is therefore most effective in the treatment of infected wounds, and because of that the danger of wound sepsis has become a thing of the past.

ACQUIRED RESISTANCE

Microorganisms have a very versatile metabolism and are capable of adapting themselves to adverse external conditions. In fact it has been known since the time of Ehrlich's work that protozoa are capable of developing resistance to chemotherapeutic substances. Bacteria show a similar behavior. It is well known, for example, that the gonococcus has developed resistance to the sulfonamides in the course of clinical treatment, and that as a result no longer responds to these chemotherapeutic substances. It is also possible to induce resistance in penicillin-sensitive bacteria, but only with special laboratory methods. The opinion is widely held and frequently expressed in the popular press that microorganisms easily become resistant to penicillin, but as far as I am aware, not a single authentic case has been reported of a genuine development of resistance to penicillin during clinical treatment. There have been some well-documented and reliable reports of a notable increase in frequency of penicillin-resistant staphylococcal infections in hospital wards during the course of time, and it is perhaps on the basis of these reports that the view has gained credence that microorganisms rapidly build up resistance to penicillin. But a careful investigation of these cases has demonstrated that they have nothing to do with the development of acquired resistance to penicillin, but are explained by the fact that two types of staphylococcus exist, one of them penicillin-sensitive and the other naturally resistant to penicillin.

In the hospital wards, where the apparent development of resistance of staphylococci to penicillin was observed originally, patients with infections caused by both penicillin-sensitive and naturally penicillin-resistant staphylococci were present. What happened during penicillin treatment was simply that penicillin eliminated all the penicillin-sensitive staphylococcal strains, but left untouched those naturally resistant; as a result of insufficient precautions, cross-infections from one patient to another with the naturally resistant staphylococci occurred, which was wrongly interpreted as induced resistance. This can be readily proved. There exists a method whereby it is easily possible to distinguish naturally penicillin-resistant staphylococci from those made artificially resistant to penicillin by laboratory methods. The penicillin-resistant strains produce an enzyme (discovered by Abraham and myself) called penicillinase, that destroys penicillin and is the cause of their resistance, while the strains made artificially resistant to penicillin do not produce this

enzyme. In the hospitals where the number of infections of penicillin-resistant staphylococci increased during treatment with penicillin, it has been shown that in all cases in which a careful bacteriologic study was undertaken the staphylococcal strains causing the infections all produced penicillinase and, therefore, were naturally penicillin-resistant. Thus, these cases offer no evidence that resistance of microorganisms to penicillin can be readily induced; and on the basis of all the information now available, the danger of rendering bacteria penicillin-resistant during the course of clinical treatment must be considered remote. In regard to this property, penicillin differs markedly from several other synthetic and natural antibacterial substances. In its astonishing combination of favorable properties, among which the difficulty of inducing acquired resistance in microorganisms is one of the most important, penicillin approaches the ideal chemotherapeutic agent, the famous magic bullet of which Paul Ehrlich dreamed.

MECHANISM OF ACTION: STRUCTURE

Penicillin is an extremely powerful bactericidal substance, but it kills bacteria only when they are suspended in a medium in which they are potentially capable of multiplying. It has no effect, even in high concentrations, on bacteria in the resting condition, e.g., if they are suspended in distilled water.

BENZYLPENICILLIN

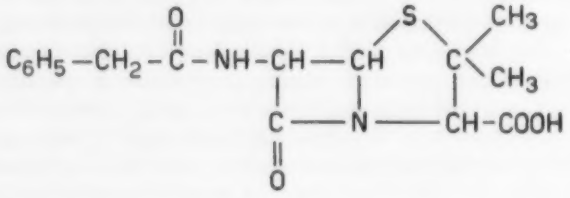


FIGURE 5.

In this respect penicillin differs from other antibacterial substances which, in sufficient concentrations, kill resting as well as growing bacteria, though in general growing bacteria are more sensitive to the action of bactericidal substances than resting bacteria. In low concentrations the action of these substances is predominantly bacteriostatic. In studies on the mode of action of penicillin, use is made of radioactive penicillin, i.e., penicillin containing radioactive sulfur. With the help of this substance it was shown that penicillin combines with sensitive bacteria while it does not attach itself to resistant bacteria. By measuring the radioactivity of sensitive staphylococci after exposure to penicillin, it could be shown that 10 molecules of penicillin per organism are sufficient to kill it.

The chemical structure of the penicillin molecule is shown in figure 5; several groups of chemists, in academic and industrial research laboratories in Great Britain and the United States, collaborated during the last war to elucidate it. The struc-

tural formula of the penicillin molecule, first proposed in 1943 by Abraham, Baker, Chain and Robinson, indicates that it is composed of two amino-acids, d-β-thiovaline and an acylated formyl-glycine, held together in a very unusual four-membered ring system, which hitherto has not been found in any other naturally-occurring substance. The great instability of penicillin and its biologic properties are due to a combined effect of the fused thiazolidin-β-lactam ring system and the side-chain.

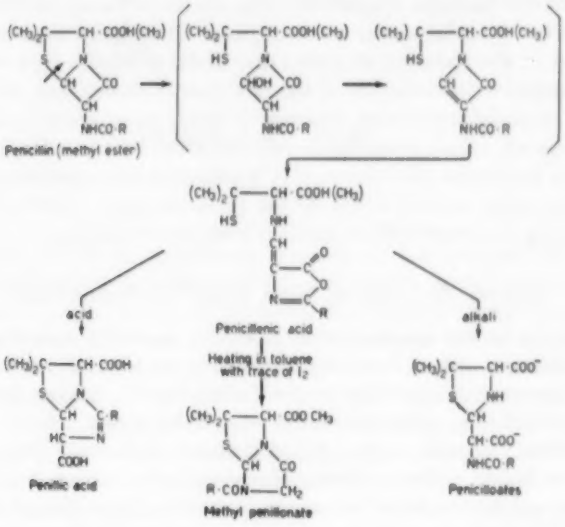


FIGURE 6.

The β-lactam ring is very stable by itself and behaves as a normal peptide bond. The first attack of inactivating substances (fig. 6) such as alkalis, acids, metallic ions, etc., on the penicillin molecule takes place on the thiazolidine ring. The opening of this ring leads to the formation of an unstable intermediate compound which, reacting with the enolic form of the peptide side-chain, rearranges to give an oxazolone intermediate, perhaps penicillenic acid. This substance, treated with alkali, is hydrolyzed to yield the open-chain derivative, penicilloic acid, or may undergo internal acylation to give an imidazoline (penillic acid) or an imidazolone (penillonic acid) derivative.

The mould *Penicillium chrysogenum* is capable of introducing various synthetic acids into the penicillin molecule, and in fact numerous biosynthetic penicillins can be obtained by adding the appropriate precursor to the culture fluid. The different biosynthetic penicillins do not differ significantly as regards their range of biologic activity, though it is claimed that patients allergic to benzyl penicillin do not show hypersensitivity to some of the semisynthetic penicillins. It is therefore particularly interesting that recently an antibiotic produced by a Cephalosporium (it was first isolated in Sardinia by Brotzu) has been isolated by Abraham, Florey and their

colleagues in a highly purified though not yet crystalline form, which behaves chemically in many respects like penicillin, showing the same instability towards treatment by alkalis and acids, giving by decomposition with mercuric chloride the amino-acid β-thiovaline (penicillamine) and being inactivated by the specific enzyme penicillinase, but different solubility properties; and it is biologically active against some gram-negative organisms, towards which ordinary penicillins are inactive. Clearly, a grouping is attached to the thiazolidin-β-lactam nucleus that gives the molecule a different biologic specificity. The chemical nature of this grouping is still unknown but is under active investigation. It contains α-amino-adipic acid. The importance of the discovery of a substance of the penicillin type which is active against gram-negative bacteria lies in the fact that it shows that the antibacterial action of the thiazolidin-β-lactam structure is much more general than had previously been supposed. Since penicillin is still the least toxic of all the antibiotics, it is obvious how important the discovery of a penicillin-like substance with a wider range of antibacterial activity could be for chemotherapy. Further developments of this interesting discovery will be awaited with great interest.

ANTIBIOTICS PRODUCED FROM OTHER MICROORGANISMS

The astonishing results obtained with penicillin naturally stimulated the search for other antibiotics, and an intensive systematic study on a very large scale on this problem commenced, especially in the United States. Among the many microorganisms examined, the actinomycetes proved to be a rich, and so far the only, source of antibiotics of wide importance in practical medicine. During this lecture we shall discuss briefly a few of these. However, before doing this, I should like to refer to some antibiotics which are not important as chemotherapeutic substances in clinical medicine but, none the less present characteristics of noteworthy biologic and chemical interest.

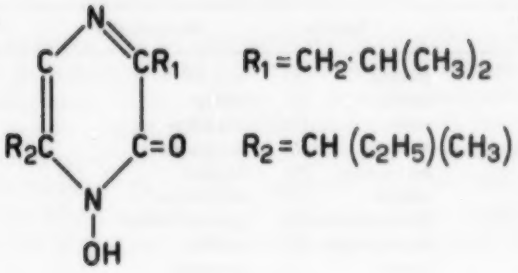
ASPERGILLIC ACID

Among the many antibacterial substances produced from penicillia and from aspergilli, I should like to draw your attention to the antibiotic aspergillic acid (fig. 7).

This substance is a pyrazin derivative containing a hydroxamic acid grouping and is the first hydroxamic acid derivative that has been found in nature. Its antibacterial activity is due to its capability of firmly binding catalytically active metals of biologic importance such as copper and iron. It thus has a mode of action similar to that of 8-hydroxyquinoline. Recently, compounds analogous to aspergillic acid have been synthesized.

ANTIBIOTICS FROM BACTERIA

A great number of antibiotics have been isolated from bacteria. All these substances have been shown to be polypeptides built up of various amino acids. The first two antibacterial polypeptides were isolated by Dubos in the crystalline state



ASPERGILLIC ACID

FIGURE 7.

in 1939 and were called gramicidin and tyrocidin. The composition of the amino acids in these substances is completely known, thanks particularly to the work of Synge, who made extensive use of the method of paper chromatography which he developed together with Martin and Consden. As can be seen in figure 8, both these antibiotics consist of simple amino acids, as are found in ordinary proteins, but some are present in the unnatural dextro-rotatory form. Gramicidin-S, also called tyrocidin, consists of five amino acids only, whose sequence has been established thus: l-valyl, l-ornithyl, l-leucyl, d-phenyl-alanyl, l-prolyl. Very probably, gramicidin-S is a cylic substance consisting of two penta-peptides of the above-named composition. Notwithstanding their apparently simple constitution, these peptides are biologically very active; they are potent bactericides and at the same time very toxic to animals. The reason for their toxicity and antibacterial activity is unknown and presents an interesting problem for the biochemist. It must be due to the structural characteristics of the cylic polypeptide unit. Recently the simple penta-peptide has been obtained by synthesis (Work) but it has been shown to be nontoxic and to possess a very low degree of antibacterial activity.

The antibacterial peptides display a notable specificity in their action, and from this point of view they recall the biologically active proteins with a high molecular

Gramicidin D		*Gramicidin S*	*Tyrocidine A*	
d-leucine	4	l-valine	d-phenylalanine	2
d-valine	2	l-ornithine	l-phenylalanine	1
l-valine	2	l-proline	l-leucine	1
l-alanine	2	l-leucine	l-valine	1
glycine	1	d-phenylalanine	l-tyrosine	1
ethanolamine	1		l-proline	1
l-tryptophane			l-ornithine	1
			l-glutamine	1
			l-asparagine	1

FIGURE 8.

Subtilin		*Mycosubtilin*
glycine	(2)	alanine
alanine	(1)	valine
valine	(1)	norvaline
leucine	(4)	isoleucine
iso leucine	(1)	leucine
proline	(1)	norleucine
phenylalanine	(1)	phenylalanine
tryptophane	(1)	proline
lysine	(3)	tyrosine
aspartic acid	(1)	arginine
glutamic acid	(3)	glutamic acid
lanthionine		aspartic acid
$C_7H_{14}O_4N_2S$		

FIGURE 9.

weight, such as the enzymes, toxins, and hormones. For example, the antibiotic subtilin (fig. 9) is very active against gram-positive bacteria, while mycosubtilin is almost completely inactive against bacteria, but very active against fungi. Since the antibacterial polypeptides have a much simpler composition than proteins with a high molecular weight, they lend themselves well to the study of the structural factors responsible for the specificity of the biologically active protein. This, of course, is one of the central problems of biochemistry, and therefore the antibacterial polypeptides have an exceptional biochemical interest, even if their practical use in medicine is limited.

Polymyxin and bacitracin (figs. 10 and 11) both have limited possibilities for clinical application, especially for the treatment of superficial infections. Their general toxicity is low, but they cause renal damage if administered over a prolonged period. Several other antibiotics of bacterial origin and peptide nature have been isolated (licheniformin, circulin, biocerin, alvein, laterosporin, colicine).

Polymyxin A and E	*Polymyxin B*
l-threonine	l-threonine
l- α-γ diaminobutyric acid	l- α-γ-diaminobutyric acid
6-d-methyl-octan-1-oic acid	6-d-methyl-octan-1-oic acid
d-leucine	d-leucine
Polymyxin C	*Polymyxin D*
l threonine	l threonine
l- α-γ-diaminobutyric-acid	l- α-γ-diaminobutyric-acid
6-d-methyl-octan-1-oic acid	6-d-methyl-octan-1-oic acid
l-phenylalanine	d-leucine
	l-serine

FIGURE 10.

Bacitracin
l-leucine
d-isoleucine (2)
d l-phenylalanine
l-histidine
l-cystein
l-glutamic acid
d l-aspartic acid
lysine
ornithine
NH_2

FIGURE 11.

ANTIBIOTICS FROM ACTINOMYCETES

We pass now to a discussion of the antibiotics which are produced from the actinomycetes, the most important ones from the practical point of view. The actinomycetes are microorganisms of the soil, for the most part nonpathogenic. There exist in the older literature many publications which show the antagonistic action of this species of microorganisms against other microbes. The actinomycetes have always particularly interested the soil microbiologist, since they are responsible for the humus formation which is of such great agricultural importance. Apart from their ability to produce humus, very little was known of their physiologic properties.

STREPTOMYCIN

At about the same time as the Oxford workers were beginning their systematic study of antibacterial substances produced from microorganisms, the American soil microbiologist Selman A. Waksman, one of the most eminent experts in the field of actinomycetes, and his co-workers started a similar study of the antagonistic properties of this particular group of microorganisms. Over the course of many years Waksman, who has devoted his whole life to the study of the actinomycetes, had succeeded in building up one of the biggest collections of these organisms in the world. Waksman and his co-workers at the beginning of their studies isolated a number of very active antibacterial substances from actinomycetes, which, however, turned out to be highly toxic and therefore could not be used as chemotherapeutic agents.

In 1944, however, Schatz, Bugie, and Waksman reported that they had isolated, as yet in crude form, from the culture filtrate of *Streptomyces griseus* an antibacterial product of low toxicity which they called "streptomycin." About a year later it was obtained in a pure form by several groups of chemists in the United States.

Streptomycin has an antibacterial activity 50 to 100 times lower than that of penicillin, but it is active *in vitro* against bacterial species on which penicillin has no effect. Among these are many gram-negative organisms including *Pasteurella*, *Salmonella*, and *B. coli*. Organisms sensitive to penicillin, such as the staphylococcus, are, in general, less sensitive to streptomycin than are the gram-negative organisms, but it is interesting that penicillin-resistant staphylococci are streptomycin-sensitive. Of particular importance is the fact that the tubercle bacillus, both the human and the bovine type, is streptomycin-sensitive.

Streptomycin, like penicillin, must be administered parenterally since it is not well absorbed from the intestine. Streptomycin is much more toxic than penicillin and, since it is less active, it must be used in higher concentrations. The toxicity of the pure product is, however, sufficiently low to enable it to act as a chemotherapeutic agent. Streptomycin must be used in the pure form, because, unlike the particularly fortunate case of penicillin already referred to, crude streptomycin preparations contain many toxic impurities which, in the early clinical trials, gave a great deal of trouble. Streptomycin, like many other bases, also gives rise to toxic effects in the pure form which are particularly marked if administration is prolonged; these are characterized by disturbances of the eighth cranial nerve and

consequent disturbances of equilibrium with vertigo, nausea and deafness, sometimes lasting several months.

Streptomycin is effective in some urinary tract infections caused by gram-negative bacteria, such as Friedlander's bacillus and *B. coli*. It is particularly effective in tularemia, caused by *Pasteurella tularensis*, and very effective in plague. Streptomycin, however, is not effective in all the diseases caused by streptomycin-sensitive microorganisms. Thus, it does not have a satisfactory action in intestinal infections such as typhoid and cholera. It is ineffective in *Brucella* infections, when given alone, but good results have been obtained by giving streptomycin with sulfadiazine.

One of the reasons why some diseases caused by streptomycin-sensitive bacteria do not respond to streptomycin treatment is the ease with which streptomycin induces resistance to microorganisms. Sensitive strains of *Salmonella*, *B. coli*, and *Pseudomonas pyocyanea* can be made resistant to streptomycin in a few subcultures made in presence of streptomycin, and acquired resistance to streptomycin is of a permanent nature. The tubercle bacillus also easily becomes resistant to streptomycin.

The development of resistance to streptomycin has often been observed during clinical treatment in tuberculosis and other diseases. The ease with which streptomycin induces resistance to microorganisms limits its therapeutic usefulness, and in the not too distant future its clinical efficacity as a chemotherapeutic agent against some of the bacterial infections in which it is now active will be reduced to an unpredictable degree. It is an interesting fact that certain bacteria, having once become resistant to streptomycin, are unable to develop in the absence of the antibiotic; for these organisms streptomycin is transformed from a potent growth inhibitor into an essential growth factor.

STREPTOMYCIN AND THE TUBERCULOSIS PROBLEM

Tuberculosis differs from the acute bacterial infections in many important aspects. The tubercle bacillus is one of the slowest growing organisms, and tuberculosis in its most common pulmonary form is a slowly developing chronic disease in which the host organism responds to the invading tubercle bacillus with a characteristic cellular response—the formation of the tubercle. This consists of compact masses of caseous necrotic tissue derived from dead tissue cells, coagulated fibrous tissue, and lipid material. Furthermore, in pulmonary tuberculosis, through the tissue destroying action of the tubercle bacilli, recesses and cavities in the lung tissue are formed.

A chemotherapeutic agent, if it is to be effective in tuberculosis, must be able to reach the tubercle bacilli wherever they are located, i.e., it must be able to penetrate into the tubercles, the destroyed tissue in the recesses and cavities, and inside the phagocytic cells, where the tubercle bacilli may remain alive for prolonged periods.

It must exert a strong bactericidal action; mere suppression of growth, i.e., bacteriostatic action is not sufficient and will result in a relapse of the disease, for the forces of natural immunity in the tuberculous host organism are much weakened and cannot be relied upon to enhance the antibacterial action of the drug. As the

complete elimination of all tubercle bacilli from the host organism must of necessity be a slow process, the chemotherapeutic agent will almost certainly have to be administered for prolonged periods of time and must therefore possess a particularly low degree of toxicity. Thus, it is clear that chemotherapy of tuberculosis is a problem which in many aspects differs from that of the chemotherapy of acute bacterial infections where the host organism does not respond with the formation of an obstacle such as represents the tubercle, and the invading pathogens are usually readily accessible from the blood stream; thus, the requirements of a chemotherapeutic agent to be effective in tuberculosis are much more exacting than those of a chemotherapeutic agent used against acute infections.

The testing of a drug for its chemotherapeutic value in tuberculosis is much more difficult than that of a drug for acute bacterial infections. No readily available experimental animal exists in which the course of tuberculosis reproduces that of the human disease. In the guinea pig and the mouse, animals frequently used for testing antitubercular drugs, the tuberculosis induced has a much more acute character than the human tuberculosis, and the lesions are more easily penetrated by drugs than the human tubercles. Both species of animals have practically no natural resistance to the tubercle bacillus and succumb to infections even if the number of infecting organisms is very small. Spontaneous recovery, as frequently happens in humans, does not occur.

For assessing the chemotherapeutic value of a drug in tuberculosis by animal experiments, it is not sufficient to establish the percentage of animals surviving the infection; a thorough pathologic study of the state of the disease in various stages of its development is necessary.

W. H. Feldman and his colleagues have made perhaps the most important contributions towards the study of experimental tuberculosis, and in a long series of painstaking investigations extending over a period of many years have laid the foundation of our present knowledge in this field and have developed many of the basic technics now universally employed for the testing of new antitubercular drugs.

Animal experiments in the field of chemotherapy of tuberculosis require a time period of many months, differing from the corresponding tests for drugs against acute infections in which results are obtained in a few days. Even from the most carefully conducted animal experiments it cannot be predicted with certainty just how a drug will behave in human tuberculosis. As I have pointed out, human tuberculosis has a more chronic character than experimental tuberculosis in animals, and the lesions formed are much more difficult to penetrate by drug than those in animals. It can be stated that while a drug which has been shown to be ineffective in suppressing experimental tuberculosis in animals has not the slightest chance of being successful as a chemotherapeutic agent in human tuberculosis, it cannot be predicted with certainty whether or not a drug which has shown encouraging results in experimental tuberculosis will prove successful in the human disease. In any case, if the disease has progressed too far no chemotherapeutic agent will be able, nor can it ever be expected, to reverse completely the lesions and to enable them to be replaced by fresh tissue. The evaluation of the chemotherapeutic value of a drug in human tuberculosis is no easy matter in view of the fact that human

tuberculosis can regress spontaneously or may respond to the classical nonchemotherapeutic methods of treatment. It can be done only on the basis of the results of a large number of cases studied under rigorously controlled conditions, and many months must elapse before such results can be collected. The greatest caution is therefore indicated toward claims of the clinical value of new drugs in human tuberculosis made without giving extensive and well substantiated evidence.

Up to the present time no drug has been discovered which could be considered as the final solution of the problem of human tuberculosis, though during recent years several developments have taken place which have given encouraging results and have brightened the prospects for the future.

It should be emphasized, however, that it is as yet by no means established with certainty that the problem of tuberculosis can be solved through chemotherapeutic methods alone. Even supposing that a chemotherapeutic agent be found with the same degree of bactericidal power against the tubercle as penicillin possesses against the sensitive staphylococcus or streptococcus, that this substance would be capable of penetrating not only the tubercle, but also the interior of the macrophages inside which tubercle bacilli survive for a long time, and, that through the bactericidal action of this substance every single tubercle bacillus could be eventually eliminated from the host organism, it is still doubtful whether this substance would produce a lasting cure for tuberculosis in the patient concerned. As the natural resistance to the tubercle bacillus is obviously very much reduced in patients suffering from chronic tuberculosis, their first fresh exposure to tubercle bacilli may lead to a reinfection if steps are not taken at the same time to raise their natural immunity. For a solution of the tuberculosis problem, it is therefore of primary importance to study and understand the factors responsible for the natural immunity of the host organism to the tubercle bacillus, in addition to looking for new antitubercular chemotherapeutic agents. A very promising line of approach in this direction has been opened by the recent work of Dubos and his colleagues on the study of antitubercular substances in tissues.

The activity *in vitro* of streptomycin against the tubercle bacillus was first reported by Schatz and Waksman in 1944. It was the achievement of Feldman and his co-workers to have demonstrated that streptomycin was effective in suppressing experimental tuberculosis in guinea pigs, even when the antibiotic was administered several weeks after the infection, that is, when the disease was already in an advanced state with well-established tuberculous lesions. A high percentage of animals treated with streptomycin survived the controls and when, several weeks after treatment, the animals were sacrificed for autopsy, it became evident that the lesions had completely disappeared or had greatly regressed. It was the first time in the history of bacterial chemotherapy that such striking results were obtained in experimental tuberculosis, and the great importance of the work of Feldman and his co-workers on the effect of streptomycin in tuberculosis—work which has now become classical—is due to the fact that for the first time it was shown that chemotherapy of tuberculosis had definite possibilities, even if streptomycin did not represent the final solution for the cure of all forms of this disease.

In further experiments carried out by other workers, it was shown that, if the

animals were not sacrificed for autopsy after treatment with streptomycin had been stopped but were left for longer time periods without administration of the drug, tuberculosis reappeared and the animals finally succumbed to the disease. This is due to the fact that, as mentioned before, the guinea pig, unlike man, has no natural resistance to the tubercle bacillus and succumbs to the smallest number of invading organisms. Evidently streptomycin, even after prolonged administration, had not succeeded in eliminating completely all the tubercle bacilli with which the guinea pigs were infected, and after cessation of streptomycin administration the remaining organisms started to grow and the infection flared up again. The clinical results with streptomycin, carried out at the Mayo Clinic by Hinshaw in collaboration with Feldman, demonstrated that acute tuberculous infections such as tuberculous meningitis responded well to treatment with streptomycin. The mortality rate in tuberculous meningitis was 100 per cent before the introduction of streptomycin and has been greatly reduced by streptomycin treatment. This terrible disease often affects children, and the success of streptomycin treatment must be considered one of the major advances in therapeutic medicine. Remarkably good results have also been obtained in the treatment of acute miliary tuberculosis, a disease which before the introduction of streptomycin therapy had a mortality of almost 100 per cent. In tuberculous infections of a chronic type, on the other hand, such as ordinary pulmonary tuberculosis, treatment with streptomycin has met with less success, especially in those cases where the lesions were already advanced. Frequently a temporary improvement is observed in patients at the beginning of treatment with streptomycin, but very often relapses occur after termination of the treatment. It was evidently impossible in such cases to sterilize completely all the tuberculous lesions with their numerous recesses and cavities, full of compact and impenetrable masses of dead fibrous tissue.

An important factor which contributes to the failure of streptomycin to eliminate all the tubercle bacilli in patients is the ease with which these organisms develop resistance to streptomycin during clinical treatment; this has been demonstrated conclusively in many cases.

The development of resistance of the tubercle bacillus to streptomycin can be considerably delayed by giving this antibiotic with other antitubercular substances, such as p-aminosalicylic acid and isonicotinic acid hydrazide. These synthetic substances are less effective clinically when used alone because they induce resistance to the tubercle bacillus even more quickly than streptomycin, but their use in combination with streptomycin has given excellent results; and, in modern chemotherapy combinations of antibiotics with synthetic antitubercular substances are employed almost exclusively.

MODE OF ACTION AND CHEMICAL STRUCTURE

Streptomycin has a bactericidal action on the organisms against which it is most active, such as *Pasteurella tularensis*. Against other organisms it is bactericidal in high concentrations, but in low concentrations it is only bacteriostatic. Its action on the tubercle bacillus, in the concentration in which it is clinically active, is

partly bacteriostatic and partly bactericidal. Its chemical structure is indicated by the formula presented here (fig. 12). It is a completely new type of antibacterial substance, similar in nature to the sugars.

The streptomycin molecule is composed of three parts: 1'1,3-diguanidino-inositol; streptose, which is a new sugar; and the nonnatural 1- form of N-methyl-glucosamine.

In view of the complexity of its structure, it is unlikely that a laboratory synthesis will be achieved. Its mode of antibacterial action is unknown.

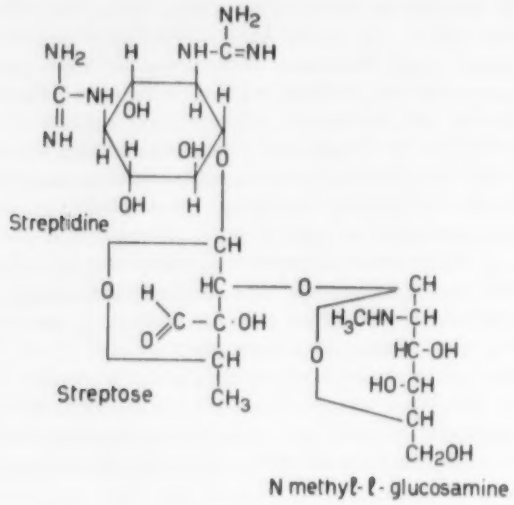


FIGURE 12.

CHLORAMPHENICOL

The antibiotic chloramphenicol, also known by the name of Chloromycetin,* is another metabolic product of an actinomycete. It was isolated in 1948 by two groups of research workers in the United States, working independently. One group, forming part of the staff of Parke, Davis & Co., together with research workers at Yale University, isolated the organism which produces chloramphenicol from a sample of Venezuelan soil; the other group, at the University of Illinois, isolated it from a much nearer source, a sample of compost soil collected near their laboratory at Urbana, Illinois. The organism was called *Streptomyces venezuelae*.

Chloramphenicol has a wide range of activity against gram-positive and gram-negative bacteria, including the *Salmonella* and *Brucella* groups. Its most interesting property, whereby it differs from the previously mentioned antibiotics, is its activity against the Rickettsiae, the causative agents of scrub and epidemic typhus. These organisms are smaller than the smallest bacteria and occupy an intermediate position

* Chloromycetin is the trade name of Parke, Davis & Company for the antibiotic, chloramphenicol.

between bacteria and the filterable viruses. Unlike the bacteria, they cannot be cultivated in the absence of living animal cells, and the anti-rickettsial action of a substance can be established only by animal or tissue culture experiments. Chloramphenicol is the first substance found to be active in Rickettsial diseases, and it therefore represents a milestone in the development of the antimicrobial chemotherapy.

Chloramphenicol can be given by mouth. It is a fairly toxic substance and there have been reports of cases of serious disorders of the blood following the use of this antibiotic—which indeed could be expected of an aromatic nitro compound. Therefore, it must be administered with caution.

The greatest value of chloramphenicol lies in its great efficacity in scrub and epidemic typhus; it is, in fact, the first chemotherapeutic substance to be active in the clinical treatment of this disease. It is also effective in typhoid fever and *Brucella* infections.

Chloramphenicol has a novel kind of chemical structure represented by the formula in figure 13. It has two unique features: the presence of (1) a nitro-benzene group and (2) a dichloracetyl group. It is the first nitro compound which has been found in nature. Its structure is relatively simple and it can be obtained by synthesis. It is the first, and so far the only, antibiotic for which it has been possible to work out an economically feasible laboratory synthesis. At present there are several methods of synthesis available, and it is also possible to synthesize numerous analogous substances which possess antibacterial properties.

Although it is possible to induce resistance to chloramphenicol by laboratory methods, so far no case of resistance developed during clinical treatment has been reported.

CHLORTETRACYCLINE AND OXYTETRACYCLINE

These two antibiotics will be considered together because their chemical structure, and consequently their biological properties, are very similar. Both these antibiotics are produced from actinomycetes of the soil, chlortetracycline from *Streptomyces aureofaciens* and oxytetracycline from *Streptomyces rimosus*. Chlortetracycline and oxytetracycline are the most recently discovered antibiotics which have found an application in therapeutic medicine. Their isolation was the result of an intensive study on the part of groups of research workers of American pharmaceutical companies, in the course of which hundreds of thousands of actinomycetes were subjected to systematic examination for their possible antibiotic activity. The organization required for the development of this kind of work on a large scale is formidable.

Chlortetracycline and oxytetracycline are active against gram-positive and gram-negative bacteria and, like chloramphenicol, against the Rickettsiae that cause scrub typhus, epidemic typhus, and Q fever.

In all these Rickettsial diseases, these antibiotics have a dramatic effect. Among the gram-positive organisms the staphylococci are particularly sensitive, including the penicillin-resistant strains. Both oxytetracycline and chlortetracycline are thus very valuable in the treatment of infections caused by penicillin-resistant staphylo-

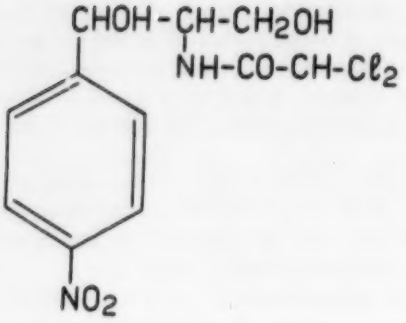


FIGURE 13. Chloromycetin

cocci. They have, in fact, been used with success in the treatment of various forms of pneumonia caused by staphylococci, Friedlander's bacillus, and other organisms. Oxytetracycline and chlortetracycline are remarkable because they are effective in true virus diseases, among which the following respond to treatment with these antibiotics: so-called atypical virus pneumonia, lymphogranuloma, and psittacosis. Thus, for the first time virus infections have become amenable to chemotherapeutic treatment.

The viruses influenced by oxytetracycline and chlortetracycline are, however, those of larger size; the small viruses, such as the common cold and influenza viruses, do not respond to these antibiotics.

During clinical treatment, resistance to oxytetracycline and chlortetracycline does not appear to develop, though it is possible by laboratory methods to render bacteria resistant to these antibiotics.

The chemical structure of oxytetracycline and chlortetracycline has only recently been clarified (fig. 14). These antibiotics, like the others already named, are a very unusual type of substance. They possess a hitherto unknown tetracyclic naphthacene ring system which has been termed tetracyclin. Both compounds are quinoid polyphenols and are representative of the only type of antibiotic whose antibacterial activity can be predicted from its structural formula. For many years it has been known that quinoid and phenolic substances, such as certain aniline dye derivatives, have a strong antibacterial activity. However, up to the present time, this class of compound has been thought useless as a source of chemotherapeutic substances, in view of their high nonselective toxicity.

The expression "broad spectrum antibiotics," which has been coined for antibiotics such as oxytetracycline and chlortetracycline, is intended to indicate a special advantage—the fact that they are active against a great variety of microorganisms, in contrast to the "more limited" antibiotics, such as penicillin, which are said to have a "narrow spectrum of activity."

However, the term "broad spectrum antibiotics" is not a particularly fortunate one. It would be more appropriate to designate these substances as antibiotics with a limited specificity of antibacterial action. Experience has shown that the wider

the spectrum of activity of an antibacterial substance, that is, the less specific its action, the greater is the toxicity; in other words, if the spectrum of activity is very large, the substance becomes a general protoplasmic poison and is therefore useless as a chemotherapeutic substance. For example, mercuric chloride is an antibacterial substance with a particularly extensive spectrum of activity, killing both macroorganisms and microorganisms. As I have already mentioned, it is known that quinones and analogous substances, some of which possess a powerful antibacterial action, must be considered as general protoplasmic poisons.

The surprising feature of oxytetracycline and chlortetracycline is not so much that these substances have an antibacterial activity, but that, despite their quinone-like structure, they are sufficiently nontoxic for internal use as chemotherapeutic agents.

That chlortetracycline and oxytetracycline are not at all absolutely innocuous substances, but have a fairly high degree of toxicity and must be administered with caution, is now abundantly clear from clinical experience. But, they are chemotherapeutic agents of undoubted usefulness with a definite place in chemotherapy. Apart from their toxicity, another undesirable effect of treatment with chlortetracycline and oxytetracycline is that it may cause changes in the bacterial flora of the intestinal tract often involving the appearance of a yeast-like organism, monilia. Although this organism is not highly pathogenic, it may give rise to unpleasant intestinal irritation, and once such an organism has become established in the intestine it is difficult to eliminate.

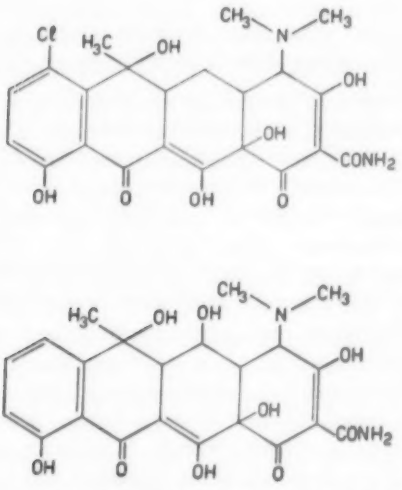


FIGURE 14. Chlorotetracycline (top) and Oxytetracycline (bottom).

The fact that it has been possible to demonstrate that quinoid phenols like oxytetracycline and chlortetracycline can be used in chemotherapy is of notable interest

and importance for organic chemistry. We may express the hope that, though perhaps the synthesis of a molecule as complex as oxytetracycline and chlortetracycline may not be possible, it may none the less be feasible to synthetize simpler quinoid phenols, having a toxicity not higher than these antibiotics, which could be used as chemotherapeutic agents. This opens up new possibilities which, without doubt, are now being intensively studied in various laboratories.

FUTURE PROSPECTS

It is evident that with the considerable number of therapeutically effective antibiotics, we now have at our disposal a formidable array of new weapons to combat successfully the majority of bacterial infections. This is indeed a most gratifying situation and signifies a brilliant success in the fight against diseases which a few years ago no one could have anticipated or even dared to hope for. However, the research for new antibacterial agents must go on with unabated vigor. The possibility of bacteria developing resistance towards antibacterial agents at present chemotherapeutically effective is a constant threat. Furthermore, it is desirable to find less toxic and more active drugs against the enteric diseases than those presently available. The chemotherapy of tuberculosis still presents a major challenge requiring a great deal of further attention. Finally, the problem of the chemotherapy of virus infections, such as influenza, poliomyelitis, yellow fever, and the common cold, which from the epidemiological point of view are more important than the bacterial infections, remains at present completely unsolved, and it is not even certain that with the present stand of knowledge it is soluble.

RESEARCH ON NEW ANTIBIOTICS, MODE OF ACTION OF ANTIBIOTICS, ANTIMETABOLITES, INTERMEDIATE METABOLISM OF MICROORGANISMS

Further advances in the field of bacterial chemotherapy will depend on general progress in the various branches of chemical microbiology, a very important section of biochemistry. Research on new antibiotics is one field of investigation which is very actively pursued at present. During the time of writing of this article, the discovery of a considerable number of new antibiotics has been announced and further development is imminent. Figure 15 shows a list, albeit incomplete, of the newer antibiotics isolated in the last years. It is particularly interesting that among these newly discovered antibiotics are some with strong action against pathogenic fungi, while some are active *in vitro* against the bacteriophages, viruses exerting a specific lytic action against bacteria. It is, of course, too early to ascertain which, if any, of the new antibiotics will find practical application in therapeutic medicine, but it is certain that a very fertile field of research has commenced which will provide sufficient problems to occupy the chemist, biochemist, and biologist for many years to come. One of the most important aspects of this work is the elucidation of the mode of action of the new antibacterial drugs which may lead to unexpected and novel approaches to chemotherapeutic problems, even if the antibacterial drugs studied have no practical application. So far, very little is known about the primary attack of any of the known antibiotics in the bacterial cells, though a number of

Antibiotic	*Empirical Formula*	*Melting Point*
Actinorodin	C_{24} H_{22} O_{11}	
Actinomycin A	C_{41} H_{66} O_{11} N_8	250° C
Actinomycin C	C_{40} H_{67} O_{11} N_7	252° C
Amycetin	C_{29} H_{44} N_8 O_9	160–165C°
Antimycin	C_{28} H_{40} O_9 N_2	139.2–140.6° C
Cinnamycin	sulphur containing polypeptide	
Collinomycin	———	280–282° C
Endomycin	———	———
Erythromycin (Ilotycin)	C_{34-36} H_{60-66} NO_{11-14}	———
Eumycin	———	———
Fradicin	C_{30} H_{34} N_4 O_4	———
Magnamycin (carbomycin)	C_{41-42} H_{67-69} NO_{16}	199.5–200.5° C
Neomycin A	C_{12} H_{26} N_4 O_5	250–260° C
Netropsin	C_{32} H_{48} N_{10} O_4	168–172° C
Picromycin	C_{28} H_{43} O_7 N	169–170° C
Resistomycin	C_{22} H_{18} O_6	315° C (decomp without melting)
Rimocidin	———	151° C
Rhodomycin (perchlorate)	C_{22} H_{30} O_{11} N Cl	198° C
Viomycin	———	252° C

FIGURE 15.

secondary metabolic derangements have been observed. It is quite possible that we do not even know at present the nature of the metabolic reactions which are interfered with by the different antibiotics. In order to make progress in this direction it is most essential to extend our knowledge about the intermediate metabolism of microorganisms and to gain a clear insight of the mode of action of the presently known chemotherapeutic antibacterial agents.

The elucidation of the mode of action of the sulfonamides by Woods to which reference was made before has led to the new concept of "antimetabolites" which promises to be a very fertile field for future developments of chemotherapy. However, most of the hitherto known essential bacterial growth factors have also an important function in the metabolism of the cells of higher animals; it would be of great importance to find bacterial growth factors with a specific function in the bacterial cell only. Here again, progress may be expected only with a better understanding of the intermediate metabolism of microorganisms.

FACILITIES AND RESEARCH ORGANIZATION REQUIRED FOR FUTURE DEVELOPMENTS IN CHEMICAL MICROBIOLOGY

Chemical microbiology is a complex field in which the closest collaboration between chemists, microbiologists, and engineers as well as special equipment is required. Antibiotics and growth factors are produced by the bacterial cell only in relatively small amounts; consequently, fairly large scale equipment, not normally available in University laboratories, is required to produce sufficient amounts of these substances to make possible the study of their chemical and biologic properties. This equipment includes large fermenters for the production of microorganisms, and the necessary extraction and processing apparatus to obtain the desired metabolic products. It is not possible to improvise this equipment. Adequate equipment is not enough in itself; of equal importance is the availability of adequately trained

service personnel in sufficient numbers to make possible the supervision of fermentations which sometimes run uninterrupted for many weeks.

So far, the main advances in the field of chemical microbiology have been made in the United States, where adequate equipment is available, mainly in the large commercial houses.

In Europe the Italian Government must be credited with having been the first to appreciate the importance of chemical microbiology for the development of modern science, and to have made available considerable funds for its development. A large research center has been built in Rome, forming part of the Institute of Public Health, the Istituto Superiore di Sanità, and it is equipped with pilot plant fermentation facilities on an industrial scale which enables any substance of microbial origin to be produced and extracted in sufficient quantities for subsequent chemical and biologic studies, and where problems of chemical microbiology can be studied adequately from the chemical, microbiological, and engineering approaches. This development was made possible due to the initiative, drive, and exceptional organizing ability of the Director General of the Istituto Superiore di Sanità, Professor D. Marotta, and has certainly raised the European scientific potential in all sections of the field of chemical microbiology. Though forming part of a Governmental Research institute and entirely financed by the Italian Government, the new Inter-

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Doctor Ernst Boris Chain was born in Berlin in 1906. He studied chemistry and physiology at the Friedrich-Wilhelm University, from which he was graduated in 1930. For the following three years he did research work in the laboratory of the biochemist, P. Rona, at the Pathological Institute of the Charite Hospital, and then, in 1933, he emigrated to England where he became a British subject.

Ernst Boris Chain

For two years Dr. Chain studied at the School of Biochemistry, Cambridge, and from 1935–1948 he was University Lecturer and Demonstrator at the University of Oxford, the Sir William Dunn School of Pathology. Here, his subjects of research were: the effect of neurotoxic principle of snake venoms on carbohydrate metabolism; tumor metabolism; various biochemical analytical methods, mechanism of the action of lysozyme, mechanism of action of spreading factor (identity with hyaluronidase).

In 1939 Dr. Chain started a systematic study of antibiotics with Sir Howard Florey. In 1940 Dr. Chain and his colleagues isolated penicillin in a form which could be injected into animals, and thus were able to demonstrate its nontoxicity and its great therapeutic effect in experimental infections in animals. The penicillin was purified and its structure elucidated. Dr. Chain also worked on the isolation of the antibiotics claviformin, proactinomycin, and helvolic acid.

Dr. Chain is currently head of the Department of Biochemistry and Scientific Director of International Research Centre for Chemical Microbiology, at the Istituto Superiore di Sanità, Rome, a position he has held since 1948. Both departments, forming part of the Chief Medical Research Centre of the Italian Government, were built and organized under his direction. He is presently engaged in research work on the development of new technics for submerged culture fermentations of penicillin, the intermediate metabolism of fungi, a study of new antifungal antibiotics, and the mode of action of insulin in intermediate carbohydrate metabolism of mammals.

In 1950 Dr. Chain was nominated Chairman of Expert Committee on Antibiotics of WHO. He won the Nobel Prize for Physiology and Medicine in 1945, the Paul Ehrlich prize in 1954, as well as numerous other medals and honors.

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national Research Centre for Chemical Microbiology encourages international scientific collaboration in the broadest sense; it is affiliated with the World Health Organization and has already extended welcome to biochemists and microbiologists of many nations.

Surveying the prodigious development of chemical microbiology in recent years we have every reason to expect with confidence that in the future, as a result of the different lines of investigations to which reference has been made, an ever increasing number of infectious diseases will be brought under control.

Chemotherapy, so brilliantly initiated by Paul Ehrlich, has grown to become one of the most potent and efficient weapons of modern therapeutic medicine, it has saved innumerable lives, and its achievements constitute a perennial and glorious monument to the genius and dynamic personality of the great scientist whose memory we are privileged to honor today.

Paul Ehrlich — as Man and Scientist

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NEW BRUNSWICK, N. J.

Paul Ehrlich, whose life-long career was devoted largely to the study of microbes and to methods of their eradication, is best known as the discoverer of salvarsan and as the "father of chemotherapy." Although Ehrlich was trained as a physician, he was not interested in clinical medicine. Instead, he did brilliant work in the field of chemistry, where he concentrated on the effects of chemical agents upon the body cells and infecting agents. Ehrlich's studies of the methods of cell staining with aniline dyes contributed greatly to our knowledge of the structure of blood and bacterial cells. His work on vital staining resulted in the development of the concept of chemical affinities (*corpora non agunt—nisi fixata*), and finally led him to the postulation of the reactions of immunity. His studies of dyes and arsenical compounds enabled him to place in the hands of the medical profession powerful tools for combating disease-producing germs, notably those causing syphilis. For the first time in the history of scientific medicine, chemical compounds capable of destroying disease-producing agents in the living body were synthesized in the laboratory. Thus were produced true chemotherapeutic agents which were capable of inflicting the greatest possible damage to the parasite with the least injury to the host or the afflicted body. As a result, the "magic bullet" and "*therapia sterilisans magna*" became bywords in clinical medicine.

Ehrlich was the first to lay emphasis upon the fact that the infecting agent may be more sensitive to treatment with chemical substances than are the infected body cells. This idea was quite contrary to the prevailing conception, as expressed by Von Behring and by many others, that the host is usually poisoned more rapidly than the infecting germs by the action of chemical agents. Ehrlich's ideas pointed a way to fundamental principles in the field of chemotherapy, which reached their particular heights with the discoveries of the sulfonamide drugs and antibiotics.

Ehrlich was born in a small town in Silesia in 1854. In school, he was a brilliant student, although his extreme modesty prevented him from asserting himself. Ehrlich's particular interests were ancient languages, mathematics, and the natural sciences. He did not care much for schoolwork and was always looking forward to returning home to his "laboratory" to study dyes and his biologic collections.

Thus, Ehrlich learned to combine theory with practice. His early observations on the adsorption of methylene blue by nervous tissue led him to postulate the potential utilization of this reaction for disease control. The story is told that when he had to write an essay on "Life as a Dream," he described life as dependent upon normal oxidation processes, nerve activity being one such process; a dream is a form of oxidation, resulting in phosphorescence of the brain. This scientific exposition

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* Based on a lecture delivered on December 5, 1951, before the New York Academy of Medicine.

by a mere youth, instead of the poetic outburst undoubtedly expected of him, failed to satisfy his examiner.

While still a young man, he became interested in the problem of staining tissues and cells. His cousin, Karl Weigert, who had already made an outstanding contribution to the staining of bacteria, aroused Ehrlich's interest in dyes and served as a model for his future scientific development.

Paul Ehrlich's experiments gave medicine the "magic bullet."

Ehrlich studied medicine at the Universities of Breslau, Strasbourg, and Leipzig, receiving his M.D. degree in 1878. At Strasbourg, he came under the influence of the anatomist Waldeyer, and at Breslau of the pathologist Cohnheim, both of whom greatly admired his zeal and scientific interest. In his early experiments, he discovered a new variety of cells, "mast cells." Ehrlich's doctoral thesis dealt with the subject "Chemical and Histological Staining Principles Using Aniline Dyes;" the youthful scientist developed the idea of chemical reactions of heterogeneous substances with the cell protoplasm, which was later to lead to his famous side-chain theory.

In his first position, as assistant in the Charité Hospital of Berlin, Ehrlich made good use of his experience in staining. His preparations of urine and blood made him famous. By the use of stained preparations, he could follow the course of disease, especially typhoid, in patients.

While listening to Robert Koch's famous announcement, in 1882, of the discovery of the *tubercle bacillus*, Ehrlich remembered the rods which he usually saw in the sputum of tuberculosis patients. He joined Koch in the further elucidation of the problem of the etiology of the disease. This was the beginning of Ehrlich's interest in bacteriology.

Ehrlich was often spoken of as a "born chemist." Only by combining a medical training and an appreciation of biologic reactions with chemical perspicacity was he able to obtain a profound insight into the problems of disease, of body immunity,

and of chemotherapy, which laid the foundation for the new science of the nature and control of infectious diseases.

His early interests in staining technics led him to a study of the distribution of dyestuffs in the animal body. As a result of these studies, he was able to differentiate and classify various types of body cells, particularly the blood leukocytes. This was followed by studies of vital staining, whereby the various dyes were found to be specific in their staining capacity for different organs or cells. As a result of these and other studies, Ehrlich concluded that "the ways and means by which drugs are distributed through the body must be of the greatest importance in the rational development of therapeutics."

In 1887, Ehrlich contracted tuberculosis. This forced him to leave for Egypt, where he spent the next two years. Upon his return, he continued his collaboration with Robert Koch, begun prior to 1887, and helped Von Behring in the latter's work on diphtheria antitoxin. He developed standards for measuring the potency of these antitoxins and clearly defined the units of their activity. Not only did he establish the principles of measurement of the activity of biologic agents, but he also elucidated the nature of the reaction whereby the body becomes immune to further infection through the formation of antibodies, or substances which tend to neutralize the infective agent or poison.

Unfortunately, the collaboration with Von Behring ended abruptly, because the latter did not give Ehrlich sufficient credit for his important contribution, which alone made possible the large-scale production and practical utilization of antitoxins.

In 1896, Ehrlich was appointed Director of the State Institute for the Control of Sera, first at Stieglitz and later at Frankfurt. Within a short time, he was made Director of the Serum Institute (1898), and finally Director of the Georg-Speyer House in Frankfurt (1906), where he remained until his death in August, 1915.

Ehrlich's most important contribution to immunology was published in 1897. His work on the fixation of oxygen by certain groupings in the protoplasm suggested to him the idea of the presence in the protoplasm of numerous other "receptors," whereby various foodstuffs are anchored prior to their incorporation in the cell. The toxins and antigens also combined with specific receptors of the cell; the cell was thus forced to replace the receptors by new ones present in excess; these finally broke off and found their way into the blood, serving as specific antitoxins or antibodies.

Ehrlich recognized the fact that serum therapy is not effective in all infectious diseases, notably those caused by protozoa and protozoan-like organisms. His future investigations were, therefore, directed largely against the latter. He first tested the possibilities of methylene blue in the treatment of malaria. Cases of tertian malaria were cured by such treatment. Although the results were not conclusive enough to justify the substitution of methylene blue for quinine, they later led to the discovery by others of the important antimalarial drugs, atebrin and plasmoquin.

In 1902, with experimental animals at his disposal, he began to develop the field of "chemotherapy," in which he laid particular emphasis on the chemical combinations of the drugs with the parasite, and which resulted in the discovery of

chemical substances which would combine and destroy, neutralize, or weaken the infecting organism without injuring the patient. This concept of chemotherapy was made possible only through the property of certain chemical substances to act selectively upon different living cells. Ehrlich made a sharp differentiation between the "parasitotropic" and the "organtropic" effect of antimicrobial agents.

Ehrlich's studies of chemotherapy included a thorough investigation of trypanosome infections. At that time there was no known cure for sleeping sickness, which was becoming a major problem in Africa. His first work, published with Shiga in 1904, was the beginning of a systematic investigation of dyes as curative agents for trypanosomiasis in mice. The result was an examination of the benzopurpurin series of drugs, which led him to the discovery that trypan red and other compounds were both curative and prophylactic in mice. This was the first cure of a disease produced experimentally in animals by the administration of a synthetic organic compound; trypan red had little practical value in the treatment of other trypanosome infections in mice. These experiments suggested the study of organic arsenical drugs, which were the culminating points of Ehrlich's contribution to medicine and to chemotherapy. No wonder that he prophesied: "I now have a dye to cure a mouse; I shall find one to save a million men."

In 1909 he discovered salvarsan, which proved to be successful in curing relapsing fever both in mice and humans. It was also found by Ehrlich and Hata to cure human syphilis and trypanosomiasis. This was the first true chemotherapeutic agent to come out of a chemical or biologic laboratory. It opened a new field in the treatment of human diseases. In introducing this drug into practical therapy, Ehrlich laid great emphasis upon the curative dose versus the tolerated dose. He finally came to recognize the importance of the single shot treatment of infections. In 1912, he introduced the more soluble derivative of salvarsan under the name "neosalvarsan." This is a condensation product of salvarsan and sodium formaldehyde sulphoxide. Careful clinical trials were carried out, and Ehrlich finally allowed these preparations to be put on the market as antisyphilitic drugs. They proved to be the greatest achievement of chemotherapy up to that time, and also showed a striking effect upon framboesia (yaws), another form of human spirochetal infection. Syphilis, unfortunately, was not so easily cured, unless treated in its early stages, especially, by salvarsan in combination with bismuth.

Ehrlich had to pay dearly, both in time and energy, to induce the medical profession to follow his detailed instructions concerning the use of salvarsan (No. 606). He fully recognized the need for observing in minutest detail the various precautions required in the use of this drug. He emphasized particularly the danger in using contaminated water. When news reached him of cases of deafness and neural relapses resulting from the use of salvarsan, he was much upset. He took it upon himself to instruct the doctors in its proper use. When he discovered neosalvarsan, some of the difficulties experienced in the use of salvarsan tended to be overcome.

Ehrlich became so enthusiastic over the results obtained with salvarsan that in 1913 he wrote: "In the next five years, we shall have advances of the highest importance to record in this field of research (chemotherapy)." It took nearly 25 years, however, before the next group of "magic bullets," the sulfonamides, were dis-

covered. These were soon followed by the "wonder drugs"—the antibiotics. Thus Ehrlich's prophesy was justified.

Between 1877 and 1914, Ehrlich published 232 scientific papers and books. In addition, more than 400 papers were published by his assistants and collaborators. Ehrlich was extremely generous with his assistants and was careful to give them full credit for their work. Many honors were conferred upon him, including the Nobel Prize, which he shared with Metchnikov in 1909.

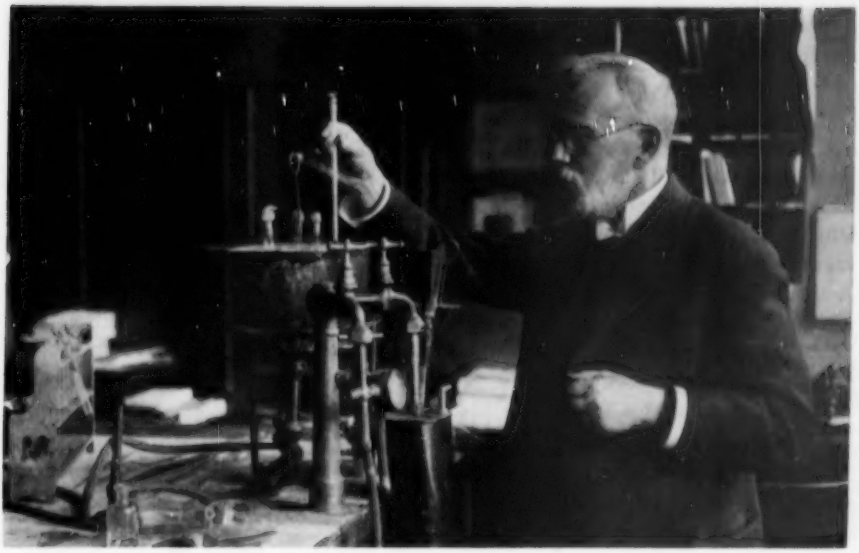
We have heard recently much discussion of the importance of "chance" versus "systematic investigations" in scientific discoveries. Ehrlich's work left little to chance. He was a great believer in teamwork, which has played such an important part in the recent discoveries of antibiotics. He expressed this as follows: "Centralization of investigation, with independence of the individual worker." He relied firmly on the careful planning of research, though the individual experiments were constantly modified as work progressed. He did not appear to attach much importance to the differentiation between "pure" and "applied research."

Despite his reliance on planned research, Ehrlich often utilized unexpected observations in the solution of given problems. On one occasion the kitchen maid forgot to remove from the stove the slides with his stained preparations of the tuberculosis organism, which were thereby greatly improved for microscopic studies. From this observation Ehrlich recognized the importance of heating slides in making certain stains. But it was his systematic, unfailing driving power and his faith in ultimately finding the right answer that produced his greatest discoveries. When, in 1908, one of his assistants tested the effect of No. 606 on experimental syphilis and reported negative results, Ehrlich was convinced that something was wrong. The next year, when the Japanese investigator Hata came to his laboratory, he was instructed to test this preparation very carefully. Positive results were obtained, fully confirming Ehrlich's expectations.

Paul Ehrlich represented the true scientist who does not sit idly by in deep contemplation, waiting for a chance to come his way but who searches for information in every branch of science that can elucidate his particular problem. In his case, he devoted time and energy to cell respiration, to the action of dyes, to problems of immunity, to the nature of malignant growths, and to the selective action of chemical agents.

After the discovery of salvarsan, honors began to pour in on Ehrlich. When his sixtieth anniversary was celebrated in 1914, congratulations from all over the world and numerous distinctions from his own and other governments came to him. The expressions of gratitude from patients cured by salvarsan only partly balanced the abuse heaped upon him by some of the physicians who were hostile to its use. The outbreak of the first world war came as an appalling shock, which finally led him to an early death.

As a person, Ehrlich was essentially an optimist. He struggled during his whole life for the advancement of human health and the eradication of disease. Although he had a hasty temper, he was innately kind. It was said of him that "he could be loved as a child." The British bacteriologist Bulloch spoke of him as the "most extraordinary man I ever met; with his wonderful inspiration, his enormous power



In this laboratory the "therapia sterilans magna" was born.

of work, his astonishing knowledge, he was the greatest man in the medical world of his time. He was modest, sincere, and noble-minded, with the greatest kindness and consideration towards everybody." Ehrlich neglected his health completely. All who knew him commented on his endless working, his continuous smoking, and the irregularity of his eating habits. He was generally indifferent to the comforts of life.

His own countryman, Richard Willstätter, another great scientist whose life and work had in some respects a certain similarity to that of Ehrlich, wrote his impressions of Ehrlich, when he came to Frankfurt on March 14, 1914, to participate in the celebration of Ehrlich's sixtieth birthday. According to these comments, translated rather freely: "Ehrlich was a simple, basically good man, whenever he had time for it. He concentrated entirely upon his indefatigable work, which drove him constantly from one experiment to another. His creative fantasy was always at work preparing him for new working hypotheses. His great capacity combined imagination with experimentation. His persistence assured success. Without being a chemist by training, he had the most unique experience in establishing the reactions of dyes in the broadest possible sense. His working cabinet, as well as his laboratory, was small. Every table and chair were covered with books, reprints, memoranda, flasks, and tubes of every possible form, and cigar boxes containing either imported cigars or tubes full of various chemical preparations. He knew and could find everything that was there, even if the search took a long time. His knowledge in his selected field was extensive and profound, although also one-sided. He could hardly

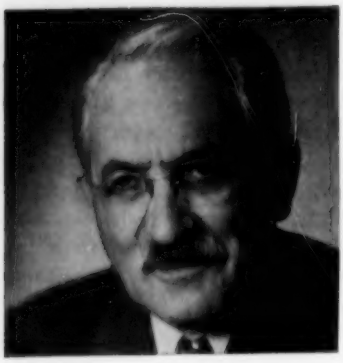
afford the time to accumulate knowledge which would not serve to advance his own selected field for science."

Miss Martha Marquardt, his secretary, described him as follows:

"Ehrlich's manner was friendly and jovial to all around him, his fellow-workers, assistants, and employees. Newcomers, or people whose work did not often bring them in contact with the Chief, were, however, often a little embarrassed and uneasy when they had to see him, in spite of his amiability. This was partly because Ehrlich's exuberant manner made it hard to grasp his meaning at first, and his directions were always given with suggestions and allusions only. Also there was a little imp in him which made him make joking remarks with an absolutely serious face, and this, with his habit of making fun of himself, confused some people who were not used to it. Those who knew him well, however, could always guess what he wanted from the slightest hint.

"Ehrlich judged his fellow-workers and employees entirely by their knowledge and ability and the work actually done, and often thought it right to ignore weak points of character. He said that the private life of those who worked with him did not concern him providing they did their duty well, and he never listened to gossip or scandal."

Ehrlich's work had a profound influence upon the development of microbiology and chemotherapy, and the fields of immunology and allergy have also greatly benefited by his fundamental experiments. Together with Louis Pasteur, Robert Koch, and Elie Metchnikov, he laid the foundation for our therapeutic war against human and animal diseases. Humanity owes a great debt to Paul Ehrlich and other chemists and microbiologists who gave of their own lives that others might live.



Selman A. Waksman

Selman Waksman was born July 2, 1888, in Priluka in the Ukraine. He completed his school training in Odessa, and immediately left for the United States, where he entered Rutgers College in 1911, receiving his B.Sc. in Agriculture in 1915. In 1916 he obtained a M.Sc. degree from Rutgers and his Ph.D. in 1918 in Biochemistry at the University of California.

In 1918 he received an appointment as Microbiologist at the New Jersey Agricultural Experiment Station and as Lecturer in Soil Microbiology at Rutgers University. He became Associate Professor in 1925, and in 1930 was made full Professor. When the Department of Microbiology was organized in 1940, he was made Professor of Microbiology and head of that department.

Dr. Waksman has isolated, together with his students and associates, a number of new antibiotics, including actinomycin, clavacin, fumigacin, micromonosporin, streptothricin, streptomycin, griscin, streptocin, neomycin and fradicin.

In May 1949, the trustees of Rutgers University voted to establish an Institute of Microbiology, and made Dr. Waksman its first director. The larger portion of the funds derived from royalties obtained from streptomycin have been assigned for the building of this Institute, which is used for research and advanced teaching, on a doctorate and postdoctorate level in microbiology.

Dr. Waksman received the Nobel Prize in Medicine in 1952 for his development of the antibiotic, streptomycin, and its usefulness in combating tuberculosis. He is an active member of the National Editorial Board of the journal, ANTIBIOTICS AND CHEMOTHERAPY.

a centennial tribute

The Mind and the World of Paul Ehrlich

(1854–1954)

*Félix Martí-Ibáñez, M.D.**

NEW YORK, N. Y.

TIME AND SPACE IN HISTORICAL BIOGRAPHY

"*Ohne hast, ohne rast.*" Without haste, without pause. The Goethean† motto of Paul Ehrlich, father of modern Chemotherapy, whose centenary physicians the world over are celebrating this month, is still an inspiration to the scientists of our time.

There are two kinds of great men in History: men of action, whose great deeds exercised an enlightening influence on their contemporaries and became a source of encouragement and inspiration for the generations to come; and men of thought, who handed their great knowledge down to posterity in their written word.

In the History of Medicine, men of action were Boerhaave and Paré, who are remembered more for their personalities than for anything else; and men of thought were Avicenna and Vesalius, whose *Canon* and *Fabrica*, respectively, were of such importance that they almost eclipsed the men who penned them.

But there are also men who leave behind them both great actions and great written works, men who soar to towering heights leaving in their wake a glorious scar on the face of the earth. Such a man was Paul Ehrlich, of whom it can be said—to paraphrase what was said of Claude Bernard in connection with physiology—that he was not a chemotherapist but Chemotherapy itself.

Our interpretation of the History of Medicine is no longer based on a conception of genius as an isolated phenomenon. Today we realize that the man of genius can be thoroughly understood only if we place him against the background of his time and his milieu. By projecting a life in time and space, we can uncover the meaning of the psychological motives behind the man and his scientific development. The scientist is also a man, a human being who lives in a certain country at a given time, and these two factors condition the genesis and significance of his work. The brain of the investigator is not a point isolated in ether; it is an organ that is subject to the influences of space and time—milieu and epoch—and it reflects the cultural complex of the age in which it lives.

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* Doctor Martí-Ibáñez is International Editor of the journal, ANTIBIOTICS AND CHEMOTHERAPY.

† Goethe's motto was similar: "Without haste, but without pause, like the stars."

THE WORLD OF PAUL EHRLICH—A GLIMPSE INTO XIXTH CENTURY SCIENCE

Paul Ehrlich was born in the middle of the XIXth century.* If our own century has been shaken by the portentous advances made in therapeutics, the last half of the XIXth century truly trembled beneath the firm tread of notable advances in the art of diagnosis. The laboratory played the all-important role then, just as the clinic does now. The late XIXth century physician lived in an atmosphere galvanized by philosophical theories. Europe was still agitated by a tidal wave of political upheavals. The governments of France and Germany had just suppressed several revolutionary movements. England, under the iron hand of Queen Victoria, tried to stanch the wounds caused by the war in the Punjab. There was a Renaissance of cultural and religious interests. The technological revolution was making rapid headway, but the horse was still a very important means of transportation and railroads had scarcely begun to embroider the planet with cobwebs of rails.

In the middle of the XIXth century, Medicine was still encyclopedic and the physician aimed at competence in all fields of his endeavor. A professor of Medicine still tried to teach all phases of Medicine. In 1848 a professor at Rostock taught clinical medicine, surgery, ophthalmology, and obstetrics! The scientific panorama was dominated by the work of Virchow the cellular architect, Pasteur the magician of ferments, and Claude Bernard the cartographer of Physiology. The importance of Anatomy in a physician's education had already been recognized, but Medicine was not yet a science. In 1850 the use of chloroform, ether, and nitrous oxide was discovered. The discovery of antiseptics twenty years later would make possible scientific surgery. The theory of the conservation of energy dominated the universe of the physicist, while Darwinian evolutionism pervaded the world of the biologist. There was a general acceptance of the supremacy of the nervous system as rector of the organism, and the old Platonic concept of the unity of the soma and psyche was reborn. Physicians were beginning to specialize, and the year of Ehrlich's birth saw the recruiting of nurses for the Crimean War.

In the 46 years which elapsed between Ehrlich's birth and the turn of the century, amazing progress was made in medicine, thus providing a historic parallel to the scientific development of Ehrlich himself. As Ehrlich grew from adolescence to youth and then to maturity, he witnessed the experimental confirmation of the bacterial origin of infections and the change from active immunization by vaccines to passive immunization by serums. The imperialistic ambitions of some nations would, paradoxically, give rise to notable advances in tropical medicine. Since the jungle held back the ambitions of Germany and England, it became necessary to defeat the jungle in the laboratory. That was the beginning of the victory over recurrent fever, dysentery, malaria, filariasis, and trypanosomiasis.

After fifteen hundred years of stagnation, the last quarter of the XIXth century witnessed the birth of modern therapeutics. In 1874 antipirin was synthesized, while the introduction of the first thyroid extracts in 1891 marked the beginnings of modern

* In Strehen, Silesia, March 14, 1854.

Endocrinology. Such therapeutic resources were soon followed by the use of radiations, vitamins, immunobiology, and psychoanalysis.

Into this medical world in ferment Paul Ehrlich was born. We must, however, bear in mind that not until Ehrlich reached maturity did the world realize that the true objective of medicine was to heal, and that although the art of diagnosis was of transcendental importance, it was not—philosophically speaking, at least—an indispensable requisite for the curing of the sick. This helps us to understand young Ehrlich's anxiety to go beyond his time and discover the cure for some of the age-old plagues that were scourging mankind. Ehrlich's scientific optimism challenged the ebbing strength of that therapeutic nihilism emanating from the famed medical school of Vienna. For almost from childhood on, the budding genius was gnawed by an obsession to find a pharmacological panacea to cure all illnesses.

EHRLICH'S YOUTH—THE SPELL OF THE BRILLIANT DYES

Paul Ehrlich was an absent-minded child and later an unsatisfactory student. It is interesting to observe how often the childhood of a genius is characterized by apparent backwardness: the superior mentality of the child prevents him from adapting himself to the absurd routines and rigid disciplines which govern the school life of his so-called "normal" companions.

Ehrlich studied medicine at the Universities of Breslau, Strasbourg, and Leipzig. His lack of concentration and excessive slovenliness caused his teachers to despair. Like Ramón y Cajal, who failed in Anatomy only to receive the Nobel Prize years later for his anatomical discoveries, Ehrlich failed in Chemistry, the very field in which he would make his name.

When he was graduated, the laboratory assistants heaved a sigh of relief at being rid of the absurd young man who was forever dabbling in dyestuffs, bespattering not only all his clothes but the walls of the laboratory. Indeed, when Koch once visited the laboratory someone pointed out to him Ehrlich's table, all smeared with dyes, and remarked that "he would never get to pass his courses."

From adolescence on, Ehrlich had been fascinated by the complicated architecture of the cell and bewitched by the modern alchemy of the laboratory. Histology and Chemistry were the springboards of his future accomplishments. Day after day his curious little myopic eyes peered through the microscope at the manifold cellular formations; then, in the laboratory he tried to ascertain the composition of the mysterious substance which filled the pale cellular profiles.

One day his cousin Carl Weigert, the indefatigable histologist from Silesia, taught him the technique of dyeing bacteria with coloring anilins. At that time researchers were beginning to stain sections of tissues from the various organs on a large scale, availing themselves of special dyes to study the different affinity of each dye for given organic cells. Histologists were intrigued by the mysterious preferences of a given coloring agent for certain tissues and thus arrived at an all-important method for differentiating one tissue from another.

During Ehrlich's student years, German industry produced an amazing number of new coloring anilins for use in textile factories. In the laboratory, the young student, his fingers and clothes forever stained with brilliant greens, blues, yellows, and reds, dyed one tissue after another, then placed them under the microscope and discovered a magic world of vivid polychromes and brilliant irisations.

Like Ramón y Cajal, whose childhood dreams about remote unexplored lands led him years later to call the brain "a matted jungle" and to enrich histopathologic terminology with an arsenal of words related to forests and fields, Ehrlich escaped from the gray monotony of his prosaic environment into the multicolored world revealed by his microscopic slides. With the passion of the lover and the zeal of the fanatic, he fused into one his two great scientific interests: Histology and Chemistry.

Ehrlich's doctoral thesis was on histological methods involving coloring anilins. When he was granted his degree in 1878, he started to work with Frerichs, with whom he spent seven years followed by a few years with Gerhardt. His first scientific undertaking was concerned with the use of his beloved coloring agents on blood and led to the discovery that different types of blood corpuscles have affinities for different staining agents. This helped him study the variable ratio of the different blood cells in infections, a method of immense diagnostic value. Ehrlich's very first sally into the scientific arena already modified and enriched Virchow's work in cellular morphology.

His next step was to study the staining of *living* tissues. At this stage he began his research with methylene blue,* another one of his precious atoxic dyes which, as it was absorbed by the tissues, revealed what happened to oxygen inside the human body. In 1885 Ehrlich published his book *Das Sauerstoffbedurfnis des Organismus*, in which he studied the need of the organism for oxygen and developed a method for studying *in vivo* intimate cellular functions.

WORK IN HEMATOLOGY

It is at this point that Ehrlich's genius shot forth over the horizon like a star-crested rocket. His method of intravital staining provided the cornerstone for modern Chemotherapy and ushered in a new era in the study of Immunity. Using the "trial and error" method, Ehrlich plunged into what he called *Spiel-Chemie*, or play-chemistry, and like a first-rate prestidigitator, he pulled out of his sleeve a series of spectacular discoveries. His "chemical imagination," or the power to conceive new paths of investigation in several different fields of chemistry, made him the greatest biochemical philosopher in History.

When Ehrlich's name is mentioned we generally think of the discoverer of salvarsan, but we should not forget that he was also the founder of modern Hematology, that he converted what was previously descriptive cellular pathology into experi-

* Ehrlich was the first to use methylene blue as a bacteriological staining agent. It has been pointed out that Ehrlich did for anilin dyes what Mayer would do ten years later for carmine and hematoxyline.

mental intracellular chemistry, and that he laid the foundations for Chemotherapy.*

When Frerichs died and Ehrlich realized that his successor Gerhardt was not interested in furthering his research, he resigned his post at the Charité Hospital in Berlin. This decision, however, was not really motivated by the lack of funds for further work. There was another reason. As a result of years of work with the tuberculosis bacilli, Ehrlich's lungs became infected. The terrifying disease suddenly threatened to cut short his career. Never is the lesson of humility that the failings of the body give us as tragic as when it is experienced by a great man. Realizing that if he stayed in cold, misty Berlin he was lost, Ehrlich decided to journey to Egypt in an attempt to regain his health.

Ehrlich remained in Egypt from 1887 to 1890. The hot sun, the dry air, and physical rest—we cannot speak of mental rest, since for genius it does not exist—produced the desired effect. A cured and eager Ehrlich left the hot, honey-colored African lands and returned to the mists of Berlin to continue his scientific adventures in the iridescent world of stained cells.

A NEW PHILOSOPHY OF IMMUNITY AND A NEW CONCEPT OF THERAPEUTICS

Ehrlich was 33 years old when he returned to Berlin. He knew that a medical practice would not leave him sufficient time for research. He decided therefore to sacrifice his financial security rather than give up his dreams. He rented a tiny apartment in a remote neighborhood of Berlin and—again like Cajal in his Madrid home—installed his own laboratory there, then alternated between his work as *Privatdocent* (he later became professor) and the search for new scientific horizons.

Once again Ehrlich's life will be characterized by the originality of his scientific undertakings. I believe that, philosophically, the human being lives by creating his own life at every step and expressing it in each one of his thoughts, words, and actions. That is why to be a *person*, in the true psychosocial meaning of the word,

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* It is not the purpose of this article to study the work of Paul Ehrlich so much as his thought and the philosophical meaning of his life. The scientific harvest of Ehrlich's mature years was rich and abundant. Let us mention here but a few of his contributions: his methods of dyeing and fixing hematic corpuscles with heat; his classification of leukocytes into acidophiles, basophiles, and neutrophiles on the basis of their granulations; his differentiation of leukemias and of myeloid and lymphoid tissues; the distinction he drew between normoblasts and megaloblasts; his demonstration that leukocytosis is a function of the bone marrow; his study of aplastic anemia; his staining of the tubercle bacillus with fuchsine; his diazoreaction of urine used for the diagnosis of typhoid; his sulfodiazobenzol test for bilirubin; his investigation of the microchemical reactions of tissues to coloring substances; his studies of the requirement of oxygen by the body, which was the seed that blossomed into his theory of side chains; his perfecting of Behring's diphtheria antitoxin; his studies on immunity in cancer; his use of methylene blue as a chemotherapeutic agent against the quartan form of intermittent fever; his use of trypan red against cow pyroplasmosis and of arsenophenilglycene in trypanosomiasis. And especially his philosophic conception of the "side chains" based on the hypothesis that the molecule of living protoplasm contains a central stable nucleus and unstable peripheral side "chains," which he called "chemoreceptors," capable of combining chemically with nourishing substances and of neutralizing toxins or poisons by throwing the loosened side chains into the circulatory system.

is to be *original*, a quality conditioned by two factors: the inner germ of originality that exists in every human being, and the historic situation—milieu and time—that surrounds the person and which may encourage the development of that originality or may paralyze it. The essence of genius has always been to impose the creative force of originality upon external conditions and, if such conditions be adverse, to rise above them, just as the great poet forges lovely verses even from his agony.

Ehrlich threw himself with characteristic enthusiasm into his study of the problems of an embryonic scientific discipline: Immunobiology. At that time scientists were beginning to give more consideration to bacterial toxins than to bacteria, just as years later in Endocrinology hormones would be considered more important than the endocrine glands. The discovery of the diphtheria antitoxin had revolutionized the cathartic theories of ancient therapeutics, for it was established that we come closer to the processes of Nature itself if instead of supplying the organism with exogenous medication we provide it with the instruments necessary to bolster its natural defenses, whether through phagocytosis or the action of the organic fluids. It was more effective to provoke active immunization through vaccines or passive immunization through serums than to attack the pathogenic germs chemically. Scientists learned, then, that in legitimate defense against any bacterial toxin, the organism created its own antitoxins. By analogy, certain poisons like ricin provoked a similar reaction of immunity in the organism.

Ehrlich studied the laws of immunity and developed various methods of encouraging active or passive immunity in infections. His studies culminated in the concept—so basic to Immunology—known as the theory of "side chains." That theory, originally formulated to explain the formation of antitoxins, led Ehrlich to conceive of the possibility of completely overcoming a toxin by *using a drug* instead of an antitoxin. In that sense, Chemotherapy was later born in Ehrlich's brain as a concept philosophically destined to complete—and compete with—Immunobiology.

Ehrlich's masterly contribution, then, was the idea that drugs could do what antitoxins did. A synthetic organic compound could, theoretically speaking, bear a side chain which would adhere to a bacterial poison or neutralize the microbe and thus destroy it. Nowadays, the word "chemotherapy" is used to designate the treatment of parasitic diseases through chemical control of the infecting agent without any marked toxic effect on the patient. But originally "chemotherapy" meant the treatment of any illness by means of a chemical agent of known composition.

Ehrlich's philosophical concepts were responsible for an immense leap forward in the historical evolution of therapeutics. For fifteen centuries, first magicians and then physicians had considered disease to be the result of some foreign body, e.g., demon, miasma, or germ, introduced into the organism and therefore to be expelled by eliminative methods—exorcisms, enemas, diaphoretics, blood-letting. The new concept of immunobiology maintained that the important thing was to stimulate and reinforce natural organic defenses. Immunobiology thus represented the historic transition between curative magic and modern Chemotherapy.

Ehrlich's work attracted the attention of Robert Koch who was already at the peak of his fame. In 1890 Koch placed Ehrlich in charge of an observation room at the Moabit Hospital containing patients experimentally treated with tuberculine. The following year, when the Institute for Infectious Diseases was founded, Koch furnished Ehrlich with fresh opportunities for work. Genius never fears genius. A great man is never afraid of surrounding himself with other great men.

Since serotherapy was making huge strides forward in a Germany that was leading the world in scientific progress, Althoff, the Prussian Minister of State, decided to establish an official institute for serum research. The *Institut fur Serumforschung* was opened in Steglitz; it had one room that had formerly been a bakery and another room that had been a stable. Ehrlich was appointed Director of the institute and was provided facilities for work Thus, his genius was "officially" recognized. Three years later the *Institut fur experimentelle Therapie* was established under Ehrlich's supervision at Frankfurt am Main; in 1906 it became affiliated with the George Speyer Institute for Chemotherapy. (Ehrlich's loyal wife had been responsible for the foundation of the Speyer Institute, for it was she who persuaded George Speyer's widow to establish an institute in memory of her husband.) And so it came to pass that Ehrlich finally saw the realization of an investigator's most cherished dream: to have a pleasant laboratory of his own and the happy tools that would enable him to fulfill all his dreams.

Dr. Paul Ehrlich in his laboratory in Frankfort am Main.

It is a characteristic of the great researcher to deviate suddenly from his original ideas; such changes may be incomprehensible to the contemporary observer, but when examined in the light of final results they seem not so much deviations as a broadening of the original horizon. Ehrlich at this point in his life decided to concentrate his efforts on therapeutics, although he never abandoned his work with coloring dyes which were as much an integral part of his soul as of his hands and clothes.

The original philosophical conception which provided Ehrlich's *point de départ* was the idea that if certain chemical staining substances possess, as we previously stated, a special affinity for given organic tissues, it might be possible to find dyes that would adhere *only* to bacteria without affecting the cells invaded by those bacteria. And if the amount of nontoxic coloring agents applied to the invaded

organism was strong enough, it might be possible to destroy *with colors* the invading microbes without harming the invaded cells in any way. Thus, Ehrlich focused his research upon the vast problem of finding staining chemical substances with an extreme affinity for bacteria and very little affinity for organic cells.

His initial results were not too encouraging. The compounds which seemed capable of killing parasites were too organotropic, while the others were not sufficiently parasitropic.

Ehrlich was then forced to work within the narrow limits of tolerated and toxic effects, and he found it necessary to discover some means of expressing the chemotherapeutic activity of the compounds for purposes of comparison. He therefore determined for each new substance the ratio between the minimal therapeutic dose and the maximum tolerated dose and called it the Chemotherapeutic Index.

That was the beginning of the decisive stage in Ehrlich's life. His laboratory became a beehive of activity. As soon as German industry brought out any new dyestuffs, Ehrlich tried them out on his laboratory animals. The fact that when he injected mice with methylene blue only the nervous system was dyed in blue, led him to the idea that he could probably inject dyes into a living animal or human being, color the invading microbes and thus kill them *with dyes*. Modern Chemotherapy really started as a true *Chromotherapy* or therapy by means of dyes.

Ehrlich's laboratory, where Jews, Prussians, and Japanese fraternized and worked happily with mice, rats, and rabbits, became an amazing center of experimentation with dyes. Every day Ehrlich and his loyal collaborators, Bertheim, Hata, and Kadereit, tested hundreds of dyes with no greater result than the conversion of papers, books, and walls into samplings of the rainbow. And as the days went by, their hands and everything around them were smeared with bright gay colors but their hearts remained dark and gloomy under the pall of discouragement.

AND THE MAGIC BULLET

It was at this juncture that Ehrlich noticed that some dyes, like the trypan red he introduced as a therapeutic agent for trypanosomiasis in mice, had a strange quality. He observed that the trypanosomes dyed by trypan red did not perish but merrily swam in a drop of blood; they lost, however, the capacity for infecting mice inoculated with these protozoaries. The reactions between chemotherapeutic agents and parasites were quite often produced *within* the human body but *were not* produced *in vitro*. This indicated that dyes tended to prevent reproduction of the germs within the human body and that the germs were then condemned to be devoured by the phagocytes or swept out with the broom of organic defenses. Thus, Ehrlich achieved the first chemical interference with bacterial reproduction and provided what is today one of the basic principles of Chemotherapy.

When Ehrlich learned that atoxil was more efficient than other arsenicals in experimental trypanosomiasis, he tried to modify the chemical structure of atoxil by making it more specifically toxic for certain microbes.

In 1905, the same year that Schaudinn and Hoffmann discovered a pale parasite,

as undulating as a small viper, that had been hidden from the human eye for many centuries and which they called *Spirochaete pallida*, Ehrlich studied the effect of atoxil on sleeping sickness. To his disappointment he discovered that besides being toxic it was ineffective *in vitro*. He then decided to modify atoxil and make it atoxic for living beings and lethal for microbes. His objective was to find an efficient treatment for sleeping sickness, the African *nagana* and the South American *mal de caderas*. One after another he developed modified compounds of atoxil which he tested in his laboratory without satisfactory results. And in contrast with other scientists who are only too ready to publish the results of even their failures, Ehrlich remained silent and continued to live like a monk.

Those were trying days. Ehrlich became a familiar sight in his neighborhood: a tiny, thin man, eternally absent-minded, simple, often impatient with himself and even more so with others, untidy, his clothes forever spotted with dyes and tobacco ashes for he was always smoking ominous-looking black cigars imported from a Broadway drugstore in New York. He never had a free hour, nor did he allow himself any amusement except the occasional perusal of a trashy detective-story magazine to which he subscribed. He scribbled formulas everywhere—on the menus of beer halls where he sometimes supped with his collaborators, on the walls of his bedroom, on any blank surface. His scientific imagination burned like a light bulb that never goes out.

On the other hand, he hated to expound his theories or write papers. As he could not avoid such tasks and was often compelled to write scientific monographs, he would shout his words incoherently while striding up and down his laboratory, and his assistants would try to put together a coherent text. In that form the work was delivered to the printer and finally published with few, if any, corrections.

Six hundred and five times Ehrlich failed. But in 1907 he developed his compound 606, which became a spectacular cure for trypanosomiasis and spirochetosis in chickens and mice as well as for *mal de caderas* in horses. What was even more amazing, compound 606, later called salvarsan or arsephenamine, could be used for treating syphilis in monkeys and rabbits.

The compound 606, or dioxy-diamino-arsenobenzol-dihydrochloride, did not kill the protozoa causing the illness *in vitro*, but only *within* the living organism when the body cells liberated the arsenic from the product injected, after ionizing it into the pentavalent form. Two years later, in 1909, the final step was taken and 606 was tried with complete success on human victims of syphilis. In a single year (1910) 65,000 injections of salvarsan were given. The whole world rejoiced. Paul Ehrlich, who had once said, "We have to learn to make magic bullets which, like those of the ancient fable, will not miss the mark and will destroy only those pathogenic agents they are aimed at," had carried out his magnificent dream. The age-old scourge, which the Renaissance poet-physician Fracastoro had named "syphilis," was curable, thanks to the genius and perseverance of Ehrlich.*

* Paradoxically, Paul Ehrlich was awarded the Nobel Prize, together with Elias Metchnikoff, for his work in Immunobiology before achieving this great victory.

Salvarsan did not turn out to be in the fullest sense the *therapia sterilizans magna* for syphilis that Ehrlich had hoped it would be, but it served to cure recurrent fever, yaws, certain forms of angina, Aleppo boil, and many epizootics.* Two years later Ehrlich developed a much more soluble and less toxic form of salvarsan—compound 914 or neosalvarsan—a new "bullet" that was added to his arsenal of magic weapons against syphilis.

Three years later, on August 20, 1915, Paul Ehrlich died. As was said when Wagner died, that day the world lost some of its value.

AN EVALUATION OF THE RESEARCHER OF YESTERDAY AND THE RESEARCHER OF TODAY

When we try, thirty-nine years after Ehrlich's death, to evaluate his work and thought, we are faced by the contrast between the Ehrlich of the first half of his life and the Ehrlich of the final years. At the end of the last century, Ehrlich stands out as the prototype of the individualistic and romantic scholar, still common at that time.

But with the years, scientific research has become "deindividualized:" it has become a collective undertaking, a matter of teamwork. The scholar has rearranged the compartments of his mind and has become a good organizer, capable of managing powerful instruments put in his hands by industry, official organizations, or university centers; he has become the captain of a team of collaborators. He is no longer the individual explorer drawing the map of a *terra incognita*. Today, he is the leader of a scientific expedition, methodically supervising the cartography of unknown lands. The old-style scientist made his very home a laboratory and workshop. Ehrlich, like Cajal and Freud, was both captain and soldier of his own personal crusade. Heir to the noble tradition of Pasteur, he did research on his own, because he was compelled by a passion for knowledge. To his work he sacrificed his personal well-being and economic security.

EHRLICH'S ERRORS

Nowadays, we frequently hear about Ehrlich's "errors." But Ehrlich's "errors" were fruitful. His theory of side chains has been criticized, yet that theory has been a heuristic principle behind Immunobiology for a quarter of a century. His 606 was not the final solution to the problem of syphilis, but it cured many other diseases. Ehrlich may have overevaluated the idea that a disease is the effect of a germ, and neglected the fact that the characteristics of an infection are especially determined by the reaction of the host and not by the nature of the parasite. But because of this concept, he sought a method of destroying parasites and converted

* My friend and teacher, Doctor Gregorio Marañón, was studying with Ehrlich in Berlin during the year of his great discovery. At Ehrlich's special request, Marañón returned to Spain carrying the rare golden powder to be used against smallpox and typhus, which in those days were decimating my native land.

his erroneous concept into a glorious truth. Perhaps he was too fond of complex theories and complicated hypotheses to refute his adversaries, thus repeating Galen's mistakes; and he was fond of quoting Duns Scotus and Saint Thomas Aquinas in his addresses to his scientific enemies, thus overwhelming them with Latinisms. But perhaps this was because the mischievousness of the child had not been completely overcome by age.

If Ehrlich was fond of complex theories, he was equally addicted to simple instruments. He reminds us of the advice Harvey Cushing once gave to a young researcher who was compiling a long list of expensive equipment for a new laboratory: "All you need to do research is running water and one idea." In Ehrlich's laboratory there was an enormous table piled high with test tubes and bottles and a lonely Bunsen burner, whose tiny flame seemed to symbolize the ever-incandescent mind of the investigator. The simplicity of his methods reflected the simplicity of his manners and his person. And Greatness is simplicity.

THE PHILOSOPHIC THOUGHT OF EHRLICH

Ehrlich's philosophic thought is a continuation of Paracelsus' thought. If the "*médecin maudit*" was the father of medicinal Chemistry in the Renaissance and if he entertained the idea of replacing Arabic polypharmacy by a few but select and powerful drugs, Ehrlich was the father of Chemotherapy and he replaced *perscrutamini scripturas* by *perscrutamini naturas rerum*. In other words, he preferred observing nature to interpreting books in the Aristotelian fashion.

It has not been sufficiently emphasized that Ehrlich's philosophy represents the revival of Paracelsus' philosophic spirit in an age of scientific materialism. At the end of the XIXth century, Paracelsus' spirit walks abroad again, impelled by the old obsession to find "specific remedies for specific illnesses." Ehrlich applied this philosophy to his work of discovering a *therapia sterilisans magna*, a sovereign remedy that with one injection would destroy invading bacteria, and towards this end he developed his side-chain theory.

This historic relationship between Paracelsus' and Ehrlich's thought is important for another reason. If antibiotics descend historically from primitive phytotherapy, once called Galenic medication, modern Chemotherapy—started by Ehrlich and continued by Domagk (1932)—descends in direct line from the heavy metals or non-Galenic medication, e.g., iron, lead, mercury, arsenic, that Paracelsus used.

The supreme lesson we derive from Ehrlich's thought is the necessity of understanding in time—as he did, and before him as Paracelsus and Descartes did—that in Science it is vain to accumulate facts and data unless one is guided by a philosophy that integrates such information rationally, interprets it, and later translates it into practical conclusions.

True science, as Claude Bernard illustrated in his *Introduction à l'étude de la médicine expérimentale* (1865), experimentally establishes a given relationship between phenomena and their immediate cause. "Therapeutics," said Claude Bernard, "will be a science only when it has established the relationship existing between the remedy

used and the cure of the sickness." That principle governs research in Chemotherapy today just as it did in Ehrlich's work.

Paul Ehrlich was able to reconcile Religion, Philosophy, and Science. He believed. He reasoned. He experimented. He sought God not in the bright light of the stars in the heavens but in the pale, cold gaslight of his laboratory. As time wears on, Ehrlich still holds out to us the *opera omnia* of his scientific discoveries, the supreme lesson of wisdom implicit in personal simplicity, and the grandeur of philosophical ideas. He observed natural phenomena and tore from them the secret of their immutable laws, which he proceeded to control. Didn't Bacon say *Natura parendo vincitur*? To obey Nature is to learn how to conquer her.

an obituary

Emanuel M. Wachtel

1912–1954

We deeply regret the sudden death of Dr. Emanuel Wachtel, who was a member of the editorial board of INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS. Doctor Wachtel died on February 10, 1954, in New York City. He was 41 years old.

A graduate of Columbia College (1933) and New York University and Bellevue College of Medicine (1936), Dr. Wachtel served his internship at Mount Sinai Hospital in New York City. Between 1939 and 1941, Dr. Wachtel was the recipient of three fellowships at Mount Sinai Hospital for the study of phospholipids, gastrointestinal x-ray, and gastroscopy. He was clinical assistant from 1941 to 1945 at Mount Sinai Hospital's Outpatient Department and Gastrointestinal Clinics and at the Metropolitan and Knickerbocker Hospitals. His research and laboratory appointments included: Assistant in Pathology, Mount Sinai Hospital, 1936–37; Research Assistant in Bacteriology with Dr. Gregory Schwartzman, Mount Sinai Hospital, 1940–41; Assistant in Gastrointestinal X-ray with Dr. Marcy Sussman, Mount Sinai Hospital, 1941–43; Assistant Pathologist, Knickerbocker Hospital, 1940–42; Chief Pathologist and Director of Laboratories, Knickerbocker Hospital, 1942–44; Assistant Pathologist with Dr. S. H. Polayes, Cumberland Hospital, 1943–44.

Between 1941 and 1951, Dr. Wachtel engaged in private practice in New York and California. From 1951 on, he was Medical Director and Vice President of William Douglas McAdams, Inc., and Medical Director of *Spectrum*.

Doctor Wachtel belonged to the American Medical Association, New York County Medical Society, New York State Medical Society, New York Pathological Society, San Francisco Heart Association, and the Medical Society of the County of Kings. He was also a member of Phi Beta Kappa and Alpha Omega Alpha.

Doctor Wachtel is survived by his wife, his children, his parents, a brother and a sister.

Tribute is due to Dr. Wachtel for his constant endeavors and accomplishments in the field of medicine. We are grieved because of his untimely death; he was indeed an outstanding Man of Science.

Quarterly Review of OPHTHALMOLOGY

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INCORPORATING INTERNATIONAL RECORD OF OPHTHALMOLOGY

FOREWORD

The objective of the QUARTERLY REVIEW OF OPHTHALMOLOGY is to bring together in one publication concise but authoritative abstracts of current articles on ophthalmology, according to an all inclusive plan which includes all special, state, and national journals as well as the bulletins of clinics, hospitals, etc., and the transactions of meetings. This embraces both the domestic and foreign literature.

To assist the reader to locate quickly the articles of current interest all data are classified and published according to the following systematic plan:

Anatomy, Embryology, Heredity, Development and Nutrition

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Conjunctiva

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Illumination and Illuminating Engineering

Ophthalmic Sociology

Education, History and Institutions

Miscellaneous

Book Reviews

Announcements

A section entitled International Record of Ophthalmology is included at the beginning of the journal. The Record Section consists of advanced clinical and experimental reports.

Quarterly Review of **OPHTHALMOLOGY**

The Effect of Tripelennamine Hydrochloride on Visual Acuity, Color Perception and Stereoptic Perception as Evaluated by the Ortho-Rater

Austin H. Kutscher, D.D.S., Neal W. Chilton, D.D.S., M.P.H., Stanley L. Lane, M.D., D.D.S., and *Eleanor E. Koepchen, A.B.**

NEW YORK, N. Y.

The soporific action of tripelennamine (pyribenzamine)[1-3] and other antihistaminic agents is well-known.[1-8] Other side effects of antihistaminics have also been reported frequently[1-13] and the overall incidence of side reactions is said to range from 10 to 60 per cent or more in patients using various preparations.[2] Because of these reactions the administration of antihistaminics to ambulatory patients has often been discouraged, particularly when it is necessary for such a patient to operate mechanical devices, or when the dulling of any of the senses or impairment of the mental processes of the individual under treatment might result in injury.

This study† was undertaken in order to evaluate accurately the action of a typical antihistaminic agent (pyribenzamine) upon visual performance. It was also intended to establish a technic for measuring visual acuity, stereoscopic perception, and color perception in the course of human pharmacologic testing procedures using an accurate optical device (the Ortho-Rater‡). Despite a voluminous literature,[14-20] mainly on its use in determining the visual fitness of applicants for industrial positions, this instrument has not been used to test the effect of therapeutic agents upon visual performance.

The Ortho-Rater is an optical instrument (fig. 1) which has been extensively used in the administration of occupational vision tests.[14, 21, 22] The measurements (in terms of scores) for the individual, along with other pertinent data, are recorded on a special card (fig. 2). Each of 12 tests represents one aspect of visual performance or visual skill. None of the tests are diagnostic in themselves. The different classifications that are possible with each of these tests are indicated on the card by a series

* The Schools of Dental and Oral Surgery and Public Health of the Faculty of Medicine, Columbia University, New York, New York.

† This study was supported in part by a grant-in-aid from Ciba Pharmaceutical Products, Summit, New Jersey. Part of this work was performed under a contract between the office of Naval Research and Columbia University.

‡ Product of the Bausch and Lomb Optical Company.

of simple numbers referred to as scores—some of which can be translated into terms of the Snellen chart (acuity). Norms have been established in terms of scores obtained in these tests, rather than in terms of corresponding clinical tests (although this latter correlation is available). Tests in the distance drum of the instrument are at the optic equivalent of 26 foot distance. Tests in the near drum of the instrument are at a downward angle and at the optic equivalent of 13 inches from the lens of the instrument (approximately 14 inches from the first nodal point of the eyes).

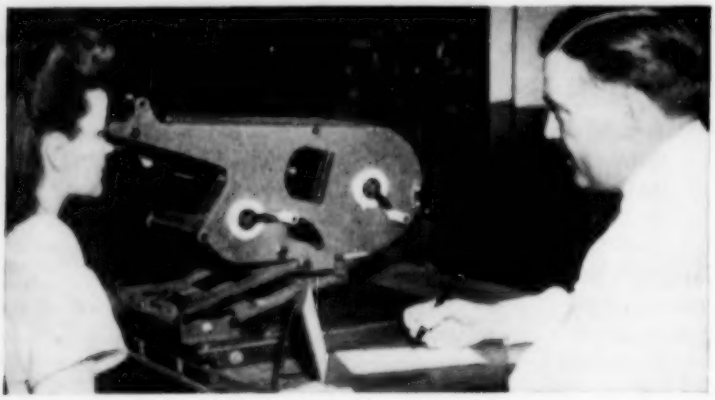

Fig. 1. The Ortho-Rater

Acuity is measured as the smallest perceptible detail in black and white discernible at a specified distance. It is tested and recorded separately for both eyes, right eye, and left eye by means of separate but fusible test fields (fig. 3) for the two eyes without closure or occlusion of either eye.

Phoria measurements indicate the lateral and vertical angles between the visual axes of the two eyes when they are not required to maintain coincidence on any

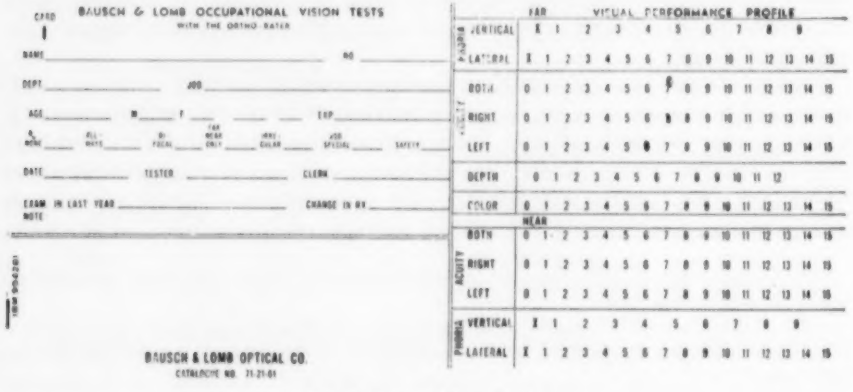

Fig. 2. Date and Score Card.

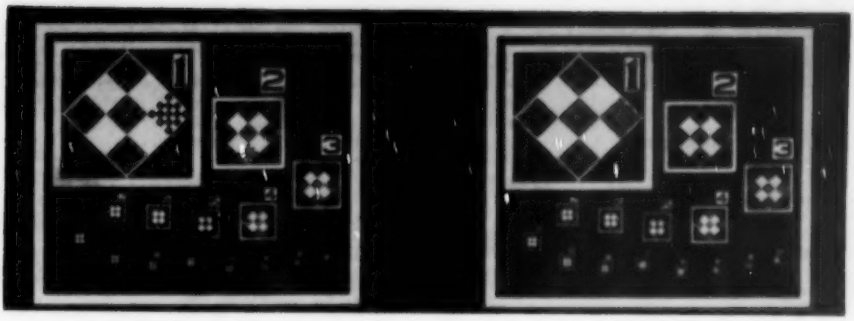

FIG. 3. Visual Acuity Test Fields.

single point of fixation, but with the eyes focused at a specific distance. Tests are made at 26 foot and 13 inch optic distances and are taken both for lateral and vertical phoria.

Depth perception is measured in terms of ability to perceive minimum differences in distances between two objects when all clues are eliminated except binocular parallax.

Discrimination of color is a measure of the least difference between colors, in different combinations, that can be perceived (entirely apart from any means for recognizing, naming, or matching specific colors).

METHODS

Twenty subjects were studied, 4 men and 15 women, aged 29 to 77. Ten patients each received an entire complement of visual performance tests (midway between meals) before ingesting a placebo tablet.* A second complete series of tests followed 1 hour and 30 minutes after ingestion of the 50 mg. placebo tablet. The third series of performance tests were made on another day, prior to the administration of a 50 mg. tablet of tripelennamine hydrochloride, and the fourth series was carried out 1 hour and 30 minutes after the ingestion of the therapeutic tablet. For the other 10 subjects the procedure was identical, but the order of administration of the medication was reversed—the therapeutic tripelennamine tablet being ingested first (between the first and second series of tests) while the placebo tablet was ingested second (between the third and fourth series of tests).

RESULTS

As determined by the procedure described previously, a 50 mg. dose of tripelennamine hydrochloride did not significantly influence the visual factors studied.

* Placebo tablets were supplied by Ciba Pharmaceutical Products, Inc., and were identical with the medicated tablet except for the substitution of inert filler for the active ingredient tripelennamine hydrochloride.

TABLE I

Results of T-tests for the Visual Characteristic Studied

Visual Characteristic	Number of Individuals Studied	Average Difference*	Standard Deviation of Difference	t†
Near acuity (both eyes)	18	−0.83	1.58	2.23
Far acuity (both eyes)	18	+0.06	1.86	0.13
Depth	17	−1.12	2.20	2.10
Near phoria (vertical)	16	−0.31	1.81	0.69
Far phoria (vertical)	17	−0.24	1.48	0.67
Near phoria (lateral)	15	−0.47	2.20	0.83
Far phoria (lateral)	17	−0.12	2.34	0.21
Color	19	−0.053	0.40	0.58

* Difference refers to: placebo before and after difference minus tripelennamine before and after difference.
† The value of t exceeded only 1 per cent of the time through chance factors is 2.88 for 18 degrees of freedom (number of individuals—1). For 14 degrees of freedom it is 2.98.

The statistical findings in this study are presented in tables I and II. The accumulated data were first analyzed by comparing the changes in the several visual tests between the before and after readings with the tripelennamine tablets. No significant differences were noted from these comparisons. For each individual, the difference between the before-and-after tripelennamine readings was then subtracted from the corresponding before-and-after placebo difference. The average of these differences was then tested for significance by the t-test (table I). In no instance was a statistically significant difference (1 per cent level) found. It will be noted that the t value for near acuity ($t = 2.23$) came closest to the appropriate critical level ($t_{1\%} = 2.90$).

In order to analyze the data further, some analyses of variance were performed, e.g., near acuity—both eyes. The only significant source of variation is that between individuals, which is usually significant with physiologic measurements. An additional feature of this table is that it yields directly the test of significance

TABLE II

Analysis of Variance of Data for Near Acuity (Both Eyes)

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square
Between individuals*	17	160.07	9.412
Between drugs	1	0.343	0.343
Between periods	4	0.348	0.348
Period-drug interaction	1	3.124	3.124
Period-individual interaction	17	13.402	0.788
Individual-drug interaction	17	17.407	1.024
Individual-drug-period interaction	17	10.626	0.622
Total	71	205.32	

* $F = 9.412/0.625 = 15.06$ which exceeds the 1 per cent value corresponding to 17 degrees of freedom in the numerator and denominator respectively.

already discussed in table II. Thus, the ratio (F) of the period-drug interaction mean square (3.124) with the individual-drug-period interaction (0.625) is 5.00, which is precisely the square of 2.23 (t).

SUMMARY

1. A procedure for testing visual changes as a result of the administration of various drugs using an optical instrument (the Ortho-Rater) is suggested.

2. As determined by this procedure employed with 20 patients, 50 mg. of tripelennamine hydrochloride does not significantly influence the visual factors studied.

ACKNOWLEDGEMENT

The authors express their appreciation to Dr. Houghton Holliday and Dr. J. W. Fertig of the Faculty of Medicine, Columbia University, and Dr. N. Franklin Stump, Director of the Consulting Services, Occupational Vision department, Bausch & Lomb Optical Company, for valuable aid and suggestions.

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NEW AGENCY FOR RESEARCH

Highlights of a paper, "Eye Research in Relation to Organizations for the Blind: A New Example of Teamwork," by CONRAD BERENS AND PHILIP S. PLATT, presented before the American Association of Workers for the Blind, July, 1953, Washington, D. C.

The affiliation of the 23 year old Ophthalmological Foundation and the 48 year old Pioneer Lighthouse of The New York Association for the Blind marked an important advance in effective cooperation between an organization for eye research and a large service agency for the blind.

The Foundation has been given suitable quarters at the Lighthouse, which has assumed responsibility for a substantial part of the financing of the Foundation. Greater efficiency and economy are expected as a result of placing the facilities and staff of the Light house at the disposal of the Foundation and of bringing the need for increased funds for medical research into the causes of blindness before the public.

The Foundation and the Lighthouse will retain their corporate identities, their separate but interlocking boards, and each will continue to benefit from the strength of the other. The Foundation, as a national organization, will continue to qualify for grants and benefits reserved for national organizations and draw support and expend funds without regard to geographic limitations.

To insure broad representation of professional men of wide experience and ability, The Ophthalmological Foundation has formed a National Advisory Council consisting of 34 ophthalmologists in 26 of the nation's largest cities.

Agencies for the blind must encourage greater activity in medical research on the causes of blindness, taking their cue from the example given by those who are raising funds for fighting poliomyelitis, heart disease, cancer, and many other diseases with their great emphasis on research.

The recent action of the Association for Research in Ophthalmology in appointing a committee to explore the possibilities and to set up an organization composed of representatives from the various foundations interested in ophthalmic research, care of the blind and prevention of blindness is encouraging. Its primary purpose is the education of the public in the need of eye research, with the ultimate hope of laying a foundation for greater collaboration and perhaps unification of effort. The group is working under the name of The Associated Agency for Research in Diseases of the Eye and Blindness.

ABSTRACTS

OPTICS, PHYSIOLOGY, AND PSYCHOLOGY OF VISION

1. *The Effect of Spectacle Lenses and Accommodation of the Depth of Focus of the Eye.* GERALD WESTHEIMER. Am. J. Optom. & Arch. Am. Acad. Optom. *30*:513–519, October 1953.

On the basis of first-order imagery, a general formula is derived expressing the depth of focus of the eye in terms of the ametropia, accommodation, eye-spectacle lens separation, the diameter of the pupil, and the diameter of the retinal blur circle. The values of the latter are related to visual acuity by the use of experimental data of Reese and Fry.

In this manner it becomes possible to draw graphs relating the depth of focus for a given acuity to the ametropia, accommodation, and pupil size. When expressed in diopters, the depth of focus is independent of object distance.

Examples are given of the application of the graphs in multifocal lens calculations.—*Author's abstract.*

2. *Some Effects of Auditory Stimuli on the Perception of Visual Flicker.* GEORGE W. KNOX. Am. J. Optom. & Arch. Am. Acad. Optom. *30*:520–525, October 1953.

Two investigations were made concerning the influence of intermittent auditory stimulation upon the perception of visual flicker. In the two experiments, patients were subjected to simultaneous auditory and visual stimuli.

Visual stimulation consisted of an illuminated homogenous surface in a dark field. Flash frequency was measured by a stroposcope connected by gears to a revolving episcotister. Auditory stimulation consisted of a 50 decibel, 1,000 cycle sound interrupted at various rates between 15 and 30 times per second by an interval timer controlled by a variable speed motor.

Experiment 1 gave negative results, showing no influence of the auditory stimulation on the visual C.F.F.

Experiment 2 showed that when visual flicker was already present, by maintaining the flash frequency below the C.F.F., the intermittent auditory stimulation increased the perceptual coarseness or pronouncedness of the visual flicker. The amount of influence was measured in terms of how much the visual flash frequency had to be increased in the presence of auditory flicker, in order to reduce the visual flicker coarseness to an amount equal to that obtained without the interrupted auditory stimulation. In this procedure variations of perceptual memory had to be given consideration.—*Author's abstract.*

3. *An Account of Recent Investigations Relating to the Luneburg Theory of Binocular Space Perception.* ALBERT A. BLANK. Am. J. Optom. & Arch. Am. Acad. Optom. *30*:374–378, July 1953.

Two recent investigations into the binocular perception of space, that of R. K. Luneburg and his colleagues and that of G. A. Fry, are discussed. Luneburg's methods, which permit ocular motility, lead to the conclusion that binocular space is hyperbolic. Fry, on the basis of observations made with fixed eyes, concludes that the space is Euclidean. The apparent contradiction may be dismissed not only on the basis of differing experimental conditions, but also because Fry's result may reflect only the locally Euclidean property of the space, rather than a property in the large.—*Author's abstract.*

4. *The Luneburg Distortion of Vieth Mueller Circles.* L. IVAN EPSTEIN. Am. J. Optom. & Arch. Am. Acad. Optom. *30*:463–466, September 1953.

The author's earlier remarks about Luneburg's theory of the binocular visual space are clarified. Luneburg claims as an experimental fact that points of light lying on a Vieth-Mueller circle will be seen in visual space as points on a circle about the center of observation. Another experiment, made by Ogle and Herzau, and using horopter rods, gives a result which conflicts with Luneburg's statement. Ogle has shown that vertical disparity plays an essential part in normal binocular space perception. The effect of neglecting this in the experimental work on Luneburg's theory is discussed. The question is raised whether vertical disparity played a part in the Ogle-Herzau experiment.—*Author's abstract.*

PHYSIOLOGY, CHEMISTRY, AND BIOCHEMISTRY OF THE EYE

5. *Nervous and Photochemical Components in Visual Adaptation.* M. A. BOUMAN AND T. TEN DOESSCHATE. Ophthalmologica. *126*:222, October 1953.

From experiments studying the influence of stimulus-area on the chance of observation of light flashes, it is concluded that the number of quanta which must be effectively absorbed by the retinal receptors in order to produce a light sensation (proved to be two for the dark-adapted eye) increases with the progress of light-adaptation. This fact indicates the presence of a nervous component in addition to the photo-chemical component in the mechanism of adaptation.

DIAGNOSTIC METHODS OF EXAMINATION, BIOMICROSCOPY AND PHOTOGRAPHY

6. *The Hand Slit Lamp—Its Functions and Techniques in Office Practice.* CHARLES C. TURNER. Am. J. Optom. & Arch. Am. Acad. Optom. *30*:505–512, October 1953.

The clinical value of the new Bausch and Lomb portable hand lamp is assessed. This instrument was found to be highly satisfactory for office use. It consists of

a lens system that projects a brilliant homogeneous narrow band of light through the anterior segment of the globe. Combined with this is a 10-X partially fixed magnifying system set at an angle of 45 degrees to the illumination system. The standard methods of illumination are summarized. The technic of observation in the zone of specular reflection is not well suited to this instrument, according to the author. Positioning of the instrument and the patient are described, and the appearance of the normal eye with the hand slit lamp is summarized.

Anterior segment abnormalities are briefly covered under the following headings: corneal opacities, corneal vascularization, keratic precipitates, aqueous flare, foreign bodies, corneal dystrophies, the anterior chamber, and the iris. The normal appearance of the lens and the appearance of lenticular opacities are described. The author believes that routine slit lamp examination is necessary on all patients prior to refraction.—*Author's abstract.*

OCULAR MOVEMENTS AND MOTOR ANOMALIES, NYSTAGMUS, READING DISABILITY

7. *The Variation of Proximal Convergence with Change in Distance.* MAX SCHAPERO AND MORTON LEVY. Am. J. Optom. & Arch. Am. Acad. Optom. *30*: 403–416, August 1953.

Eight subjects, with an average age 28.5 were selected at random. Using a phorometer mounted on a floor stand and trial case lenses, a series of phorias were taken at six distances, 6 M., 2 M., 1 M., 50 cm., 40 cm., and 33.3 cm. Six accommodative demands were presented at each 00.00 D., 0.50 D., 1.00 D., 2.00 D., 2.50 D., and 3.00 D. Corrections were made, employing a formula devised by Hofstetter, to determine the actual convergence from the centers of rotation for each accommodative demand. Graphs were constructed for each subject, plotting convergence against accommodative demand, and one composite graph was constructed for averages of the 8 subjects.

Results: Variations with subjects as to amount of proximal convergence present; the distance it first becomes manifest; and its rate of change with change in distance. Generally it increased with decrease in distance. Average amounts found were: 1.8Δ at 2 M., 1.9Δ at 1 M., 2.3Δ at 50 cm., 3.2Δ at 40 cm., and 3.0Δ at 33.3 cm. A decrease in slope was evidenced as the distance decreased, resulting in interlacing and meeting of lines at the upper accommodative demands, with less proximal convergence found at these upper levels. It is felt that a truer picture of proximal convergence was present at the lower accommodative demands, and not by considering over-all averages. Present at the 0.00 D. demand was 1.5Δ at 2 M., 3.0Δ at 1 M., 3.5Δ at 50 cm., 3.9Δ at 40 cm., and 4.6Δ at 33.3 cm. Proximal convergence, on the average, becomes a clinical entity at 2 M., or even further, and increases in an accelerated manner as the distance decreases. Exploring the changes in slopes further, 3 subjects were tested at 4 M. and 33.3 cm. distances, with accommodative demands up to 6.00 D. The same trend was obtained. Higher clinical gradients at further testing distances than at nearer testing distances were

found, as was a tendency to have higher gradients at higher accommodative demands than at lower accommodative demands, especially at the further testing distances. The following speculations as to the cause of this relationship were made: (1) The depth of focus permits a play in accommodative response, either more or less than demanded. (2) The change in pupil size with increased accommodation and convergence provides an even greater depth of focus, allowing greater freedom of accommodative response. (3) Creating accommodative demands greater or less than normal for a certain distance may alter the pattern of accommodative response. (4) The relationships of accommodative response to the demands may vary at different distances, e.g., being on the maximum side of the depth of focus at 6 M. and on the minimum side at 33.3 cm. (5) A real change in gradient occurs from attempts to meet difficult accommodative demands or from fatigue. (6) Fusional convergence may be introduced at certain accommodative demands which were difficult to meet (as −3.00 D. at 6 M.). (7) The addition of kinesthetic clues at the near testing distances may alter the response. (Subjects were required to hold the target support at the three near testing distances.) (8) Changes in perceived size from the effects of the test lenses may have altered the accommodative response.—*Author's abstract.*

8. *Seeing and Reading.* DONALD L. CLELAND. Am. J. Optom. & Arch. Am. Acad. Optom. *30*:467–481, September 1953.

The constant demands made upon the visual mechanism during the reading process have received the attention of many researchers, educators, and eye specialists. The author reviews some of the research that deals with word perception, the mechanics of reading, visual factors that may or may not differentiate a good reader from a poor one, certain factors of topography that may affect the reading process, and finally, the extensive research conducted by Doctors Carmichael and Dearborn to determine whether or not prolonged reading causes visual fatigue.

The last study mentioned supplies interesting data in regard to the reading of projected microfilm, the rate of reading, duration of fixation, amount of regression, and the span of recognition in reading two different types of material; material that, for the average reader, may be classified as easy and fairly difficult.—*Author's abstract.*

9. *An Investigation of the Time Characteristics of Accommodation and Convergence.* MERRILL J. ALLEN. Am. J. Optom. & Arch. Am. Acad. Optom. *30*: 393–402, August 1953.

The equipment and technic of studying the accommodation response and the associated convergence response are presented. An instantaneous determination of accommodation was made at a selected time during an accommodative response by means of a flash exposure from a modified Fry optometer. One measurement of accommodative achievement was made during each accommodative act. Convergence was recorded photographically. No optic stimulus to convergence or fusion was supplied. The results obtained showed the reaction time of accommo-

dation tended to be greater by about 0.10 second than the reaction time of the induced accommodative convergence. Reference is made to a supporting study on the latent period of the ciliary muscle.—*Author's abstract.*

CORNEA, SCLERA AND TENON'S CAPSULE

10. *Posterior Half-Incision of Cornea for Astigmatism.* TUTOMU SATO. Am. J. Ophth. *36*:462, April 1953.

Severe astigmatism, astigmatism of slanted axis, and all other forms which cannot be corrected by glasses may be treated by Dr. Sato's posterior half-incision of cornea. In his experience, the operation is indicated for all astigmatisms over two diopters.

CONJUNCTIVA

11. *Operative Behandlung des trachomatösen Symblepharons.* ZVONIMIR PAVISIC. Ophthalmologica. *126*:240, October 1953.

The development of trachomatous symblepharon is described. First the symblepharon anguli interni develops, then the symblepharon posterius of the lid. To prevent further progression of symblepharon in trachoma, a plastic operation is recommended to free the symblepharon with implantation of a flap of oral mucosa onto the eyeball to re-establish the temporary fold. This procedure was carried out with good results in 3 cases of trachomatous symblepharon.

UVEAL TRACT AND SYMPATHETIC OPHTHALMITIS

12. *Endogenous Uveitis in Children.* M. D. DAVIS. Arch. Ophth. *50*:443, October 1953.

The occurrence of active endogenous uveitis was observed in 5 girls and 7 boys between the ages of 5 and 15 years. The disease was diagnosed as chorioretinitis without anterior segment involvement in 2 of the 12 patients, and as iritis or iridocyclitis with or without posterior involvement, in the remaining 10. Of these 10, 4 patients had definite concurrent rheumatoid arthritis and 2 had a history of arthritis without any residual joint deformity. No other causative factor was noted in any of these patients, except for sarcoidosis in one. The cause was undetermined in the remaining 4 patients. The anterior uveitis was of granulomatous type in 2 patients, nongranulomatous in 3, and of quiet serious type in 5. This last type was noted in most of the cases of iritis associated with juvenile rheumatoid arthritis collected from the literature. Of the 5 patients with this last type of anterior uveitis, 3 had definite rheumatoid arthritis, 1 had a history of arthritis, and in one the cause was undetermined. Described in detail are 2 patients with anterior uveitis, associated with typical rheumatoid arthritic deformities of the proximal interphalangeal joints bilaterally and sarcoid lesions on the extensor

surfaces of both arms in one, and with synovial thickening of the enlarged right knee joint in the other. A brief review of the literature on the triad of band-shaped keratopathy, iritis, and juvenile rheumatoid arthritis is presented, and the association of rheumatoid arthritis with juvenile uveitis is stressed.

CRYSTALLINE LENS

13. *Beitrag zum Studium der Cataracta centralis.* A. KONSTAS VON KONSTANTIN, Saloniki. Ophthalmologica. *126*:230, October 1953.

Three cases of *cataracta centralis congenita* are described in two sisters and the daughter of one of them. The family tree in question shows dominant inheritance. The differences seen in size and formation of individual opacities are believed to be variations in the manifestation as regards size and formation, and are related to a certain "liability" of the diseased lens gene. The forms of *cataracta centralis congenita* described in the literature under different names are taken to be variations of one and the same basic form. For all these forms, the collective name of *cataracta centralis congenita disciformis* is proposed. In conclusion, the individuality of *cataracta centralis congenita* is emphasized and the clinical separations of this form of cataract is justified.

14. *Cataracts in Galactosemia.* ARNALL PATZ. Am. J. Ophth. *36*:453, April 1953.

An analysis of the cataracts observed in reported cases of clinical galactosemia is tabulated. The most commonly observed opacity appears as a central refractile ring resembling the "oil drop" effect of lenticonus. Clusters of cortical vacuoles and various forms of zonular cataract have been observed.

In view of the rapid cataractogenic effect of galactosemia, periodic examinations by the ophthalmologist are advocated in the management of these patients. The appearance of new lens opacities probably indicates a failure to maintain a strict galactose-free regimen.

Critical observations on experimental glactosemic cataracts revealed that temporary galactosemia does not interfere with the ability of the rat lens to form healthy new fibers after termination of the galactosemia.

The ocular findings in three galactosemic patients who have been followed over a period of from 11 months to five years are presented.

EYEBALLS, EXOPHTHALMOS AND ENOPHTHALMOS

15. *Aspiration Biopsy in Intraocular Tumors.* J. C. LONG, W. C. BLACK, AND R. W. DANIELSON. Arch. Ophth. *50*:303, September 1953.

Aspiration biopsy makes possible the reliable determination of the presence of malignant growths within the eye. The specimen obtained permits a cellular classification of the tumor. If a positive diagnosis is obtained after biopsy, the eye should immediately be enucleated. If the eye is hopelessly lost, regardless of the diagnosis, enucleation without biopsy is indicated.

Aspiration biopsy of intraocular lesions was attempted in 11 eyes; a diagnosis of intraocular malignant neoplasm was made in 7 cases of malignant melanoma and in 2 cases of retinoblastoma. In the 2 remaining cases, the aspiration contributed to the diagnosis. In 8 of these cases the aspiration was conducted immediately after enucleation as a means of evaluation of the method. The possibility of increasing the danger of metastasis or local recurrence by the procedure is discussed. It is felt that aspiration biopsy should be reserved for the infrequent case in which enucleation would not be indicated unless a tumor were present and in which intensive study has not made possible a positive diagnosis.

GLAUCOMA AND HYPOTONY

16. *Present Status of Goniotomy.* OTTO BARKAN. Am. J. Ophth. *36*:445, April 1953.

Goniotomy performed on 178 eyes afflicted with infantile glaucoma preserved useful vision in most cases. In 129 eyes, pressure was normalized and vision maintained or restored. In those cases in which the diagnosis was made early, the operation insured vision sufficient to permit the child to attend ordinary schools. The operation was unsuccessful in 26 eyes.

In the past three years, by virtue of improvements and simplifications in technic, it has been possible to operate with the glass under gonioscopic control on eyes in which this procedure would formerly have been impossible.

A case of glaucoma associated with aniridia was operated successfully by goniotomy.

A plea is made for the early diagnosis of congenital glaucoma and for prompt, adequate operation by goniotomy. The operation should be performed under gonioscopic control whenever possible. If, soon after onset, increased intraocular pressure is normalized by goniotomy, transparency of the cornea is almost completely restored and maintained, and vision is afforded an opportunity to develop. The urgency of prompt relief of the increased pressure is stressed.

17. *Dibenamine: An Experimental and Clinical Study.* S. L. DELONG AND H. G. SCHEIE. Arch. Ophth. *50*:289, September 1953.

The authors present certain experimental data concerning the mechanism of dibenamine in lowering intraocular pressure in patients with acute glaucoma. Dibenamine, a nitrogen mustard derivative, is known to have highly potent sympatholytic and adrenolytic properties.

Dibenamine produced no change in the passage of systemically administered inulin or para-aminohippurate across the blood aqueous barrier in animals. Significant decreases in the flow of aqueous from animal eyes under constant pressure were caused by dibenamine. The administration of dibenamine prevented the attainment of peak pressure in animal eyes with air glaucoma and significant reduction in ocular tension in three of five human eyes with clinical acute glaucoma.

The authors conclude that the evidence presented suggests that dibenamine causes a decrease in the formation of aqueous humor.

PHARMACOLOGY, TOXICOLOGY, AND THERAPEUTICS

18. *An Early Symptom of Streptomycin Neurotoxicity.* L. S. SANNELLA. Arch. Ophth. *50*:351, September 1953.

In normal persons a slight motion of objects in the visual field is in a direction opposite to the movements of the head. If glasses are worn which are a correct focus for the distance observed, the motion is minimal but increases if the glasses are removed. It is therefore possible that in the presence of an irritated labyrinth the normal illusory movement on passive motion of the eye (on turning the head voluntarily) becomes intensified.

If this hypothesis is correct, nystagmus might be produced in persons with early streptomycin toxicity by stimuli which would not produce it in normal persons.

The phenomenon is possibly the earliest symptom of streptomycin toxicity in the nervous system. To the untrained observer this neurotoxic effect might be described as lightheadedness, dizziness, or instability of vision. The symptom appears from days to weeks before the signs of gross vestibular damage and may subside without progressing to such damage. The lack of progress and disappearance without vestibular impairment in certain cases may be related either to the small daily dose or to the use of dihydrostreptomycin, rather than streptomycin.

Research for a less subjective, or more accurate, method of measuring this phenomenon should be instituted to add to the basic knowledge of vestibular-oculomotor interrelations.

19. *Diabetic Retinopathy Treated with Testosterone.* R. H. BEDROSSIAN, D. S. POCOCK, W. S. HARVEY, AND A. S. SINDONI. Arch. Ophth. *50*:277, September 1953.

The authors selected 77 patients of both sexes with diabetic retinopathy from the metabolic clinic of the Philadelphia General Hospital for this study. Twenty-six patients received saline injections, and 51 patients were given either testosterone or a combination of testosterone and estradiol in weekly intramuscular injections. The patients had periodic funduscopic examinations during the course of treatment and at the end of therapy (approximately 20 weeks' duration).

The conclusions drawn from this study were: (1) Hormone therapy with testosterone propionate or testosterone propionate and estradiol in weekly intramuscular injections, given for five months under specific conditions of the study, was not demonstrably more effective in the control of diabetic retinopathy than were weekly injections of saline. (2) The data indicate that weight, race, duration of diabetes, and type of insulin did not affect the results of treatment. The effects of the patient's age and the insulin dose were equivocal.

20. *Effect of Physostigmine and Pilocarpine on Iris Sphincter of Normal Man.* O. LOWENSTIEN AND I. E. LOWENFIELD. Arch. Ophth. *50*:311, September 1953.

Individual differences exist in the degree of miotic effect of both pilocarpine and physostigmine in various human subjects. These differences in sensitivity are shown in all factors which constitute the contraction curve, such as the latency period before contraction, speed of contraction, degree and duration of contraction, speed of redilation, and subjective sensations, such as pain. The existence of individual variations other than those shown in the survey may be expected, since the results were collected in experiments on only 6 patients. Small doses of pilocarpine hydrochloride alone (1 drop of a 0.1 per cent solution) are less effective than small doses of physostigmine salicylate alone in a similar concentration of 1 drop of a 0.1 per cent solution.

The combined administration of small doses of pilocarpine and physostigmine is generally more effective than instillation of either drug alone; the effects of physostigmine and pilocarpine on the pupils are additive, and not competitive; therefore, no decreased effectiveness of anticholinesterase may be expected to follow the application of pilocarpine.

The pupillary reflex to light persists after pilocarpine has produced miosis. Further contraction to light disappears only when the pupil becomes so small that it has reached the mechanical limit. Even a pupil of 1.75 mm. diameter still shows traces of further contraction to light.

These observations indicate that pilocarpine as such does not inhibit the effect of physiologically produced acetylcholine. Acetylcholine and pilocarpine have supplementary, and not competitive, effects.

The extent of the pupillary reaction to light under the influence of miotics is parallel to the degree of miosis existing at the moment of stimulation; it does not depend upon the type of drug which produces the miosis.

These results refer to human subjects only; however, earlier experiments on monkeys and cats showed that in respect to the pupils, no competitive effect between pilocarpine and acetylcholine existed in these animals.

An additive action of pilocarpine physostigmine and physiologic acetylcholine was shown in relation to their miotic effect only; these results may, but do not necessarily, apply to the more complex hypotensive effect of the drugs tested.

COMPARATIVE OPHTHALMOLOGY

21. *The Electric Responses of the Eye. Part I: Responses of Single Photoreceptors.* DAVID D. MICHAELS. Am. J. Optom. & Arch. Am. Acad. Optom. *30*:451–462, September 1953.

This is the first in a series of papers dealing with the electric responses of the eye. Following a brief historical introduction, the experimental data concerned with the electric responses of individual photoreceptors is reviewed. The discussion is primarily confined to the responses of the invertebrate *Limulus polyphemus*, in which

each photosensitive cell is directly connected to a single nerve fiber without any intervening synapses. The characteristics of the nervous discharge are then compared to the photochemical changes known to occur when these cells are stimulated. It is concluded that such a comparison yields remarkable agreement with respect to such phenomena as light and dark adaptation, Weber-Fechner function, visibility curve, and the reciprocity relation expressed by the Bunsen-Roscoe law. This means that the more intricate (internuncial) neuron arrangements found in complex retinas may be expected to produce effects which are on the order of modifications and additions, rather than the fundamental mediation of nonchromatic stimulation.—*Author's abstract.*

22. *The Electric Responses of the Eye. Part II: Optic Nerve Responses of Complex Eyes.* DAVID D. MICHAELS. Am. J. Optom. & Arch. Am. Acad. Optom. *30*: 526–535, October 1953.

This is the second in a series of papers on electric responses of the eye. The characteristics of the optic nerve discharge from eyes containing retinal internuncial neurons are reviewed and compared to responses of an eye which does not contain internuncial cells. The analysis of response by the microdissection and microelectrode technic is described. The types of responses are considered in relation to fiber autonomy and stimulus variables, and some recent studies bearing on this problem are presented.—*Author's abstract.*

OPHTHALMIC SOCIOLOGY

23. *The Preschool Blind Child and his Needs.* BERTHOLD LOWENFELD. Exceptional Children 50–55, November 1953.

Since 1942, when the late Dr. T. L. Terry of Boston first reported on retrolental fibroplasia, there has been a steady increase in the number of young blind children. On August 1, 1953, services for preschool blind children by the California State School for the Blind were provided to 206 cases in southern California alone, of whom 150, or 73 per cent, were blind because of retrolental fibroplasia. The number of preschool blind children in the entire state is estimated at about 600.

Parents of a preschool blind child find themselves in a situation for which they are emotionally and pedagogically unprepared. The training of a blind child must be based on the fact that his needs are basically the same as those of children with normal vision, although some special adjustments must be made because of his visual handicap. The parents' attitudes toward their child and their feelings about him are the most influential environmental factors and are more important to the development of a healthy personality than the particular technics used in rearing the child. Parents need assistance in finding their child medical and educational facilities according to his age and needs. Also necessary is interpretation of the blind child's capabilities and needs to the local community and its facilities. Services for preschool blind children have shown a steady growth since 1952. It is

almost unanimously agreed that programs of visiting teachers are the essential core. This home visiting and counseling program offers continuous guidance to families through periodic visits scheduled according to the needs of parents and children.

Placement in regular nurseries and kindergartens and in special day nurseries for blind children are discussed, as is group work with parents. The residential nursery for blind children has a limited function in the education of blind children, as it does in that of normal children, since separation from the family during the first years of life should be resorted to only if it is a necessity. There is also a need for counseling services in the hospitals and clinics where diagnosis is likely to be made. This is particularly important because it would be available to the parents at the time when they are informed about their child's visual handicap and may be in greatest need of services such as interpretation and psychiatric consultation.—*Author's abstract.*

MISCELLANEOUS

24. *Ocular Toxoplasmosis: Contribution to the Study of Ocular Symptoms in Infant Toxoplasmosis, Proved by the Finding of the Parasite.* J. LAVAT, Faculté de Paris. Chibret Prize, 1953.

Ocular signs in the congenital and early postnatal toxoplasmosis are of primary importance. They are manifold and may present a highly characteristic syndrome.

Microphthalmia and pendular nystagmic movements of the eyeballs are frequent signs often associated with strabismus, which is usually convergent, and iridocyclitis. The lens and the vitreous are usually normal.

The chorioretinitis is the oustanding finding, presenting a characteristic picture. Most frequently it produces pseudocoloboma of the macula caused by severe chorioretinitis of the posterior pole in its cicatricial stage. An intermediary stage beginning with central atrophy and pigmentation may also be fairly characteristic. Occasionally, lesions may assume the form of retinal separation without pathognomonic characteristics, or with pseudogliomatous or even peripheral cystic aspects, surrounded by chorioretinitis.

Histopathologic studies reveal that the choroid is generally less affected than the retina, and that the involvement seems to be secondary. It may be infiltrated by edema fluid and cells; it rarely contains the toxoplasma organisms. Usually the most pronounced lesions are found in the choriocapillaris, adjacent to retinal lesions.

The retina is most commonly involved, and the optic nerves and sheaths are less frequently affected, usually by a relatively limited inflammatory reaction.

The diagnosis of toxoplasmosis is difficult. It cannot be definitely made without identification of the parasite, even when it is suspected in a patient with chorioretinal lesions that appear to be characteristic. In the absence of a direct proof, the diagnosis must depend upon the clinical findings and on indirect immunologic

methods of diagnosis. If these are negative, diagnosis is rendered doubtful in recent cases, but cannot be excluded in old lesions.

The examination of the patient by Lavat revealed nystagmus, variable strabismus, relative microphthalmas, and slightly pigmented chorioretinal lesions in the form of ovoid plaques, one in the macula, one nasal, and another in the inferior part of the retina. The findings were suggestive of a typical coloboma. Intracranial calcifications and strongly positive serology were found.

The diagnosis was made during life and was confirmed by histopathologic examination of the brain which revealed pseudocysts.

25. *Epitheloidzellige Granulomatose (Boecksches Sarkoid) an der Bindehaut.* VON H. KRÜMMEL. Ophthalmologica *126*:193, October 1953.

A report is presented of 7 cases of epitheloid cellular granulomatosis on the conjunctiva of the lid. Six patients had a Boeck sarcoid of the skin; 3 had the same disease of the lung which partly developed into tuberculosis; 2 had an ostitis cystoides; and one of them also showed residues of a Heerfordt syndrome, which was the only sign of illness in this patient. Excisions of pieces of conjunctiva were worked up histologically. They showed, besides the nonfusible, knotty epitheloid cell conglomerations reported in the literature, a differentiated new formation of argentophile fibres. The syncytium of the cells and fibres had all the morphologic characteristics of a typical reticulosis.

26. *The Effect of Stimulus Size and Retinal Illuminance on the Human Electroretinogram.* LT. COL. ELWIN MARG. Am. J. Optom. & Arch. Am. Acad. Optom. *30*:417–433, August 1953.

This paper describes the changes in the amplitude of the human electroretinogram (ERG) with varying retinal illuminance and stimulus size. The data are reviewed with particular reference to the effect of stimulus area on the ERG when the total luminous flux is constant.

Measurements were made with both an A.C. and a special converter (chopper) D.C. amplifier which used z-axis modulation of the cathode ray oscilloscope. Possible distortions of the A.C. amplifier were evaluated with the D.C. system. The electrodes were mounted in a contact lens on the eye and in a rubber cup on the forehead. The stimulus apparatus provided a "Maxwellian view" with variable size from 5 to 41 degrees and luminance up to 2600 millilamberts.

As the size of the stimulus is increased, a marked change occurs in the ERG. Curves are presented to illustrate the course of the *a*-, *b*-, and *b'*-waves. The latter is a negative after-*b*-wave which may be part of the illumination potential of the retina.

As the retinal illuminance was varied with different size fields, it was found that the luminous flux appears to be constant for the position of the maximum of the *b*-wave plot regardless of the size and luminance of the stimulus, within error of measurement. However, the height (EMF) of these curves appears to be a function of area, becoming smaller with fields of increasing size. Hence, while stray (non-

focal) light is the primary stimulus in the ERG, an effect of area (focal light) appears to be demonstrated.—*Author's abstract.*

BOOK REVIEWS

Vision: Its Development in Infant and Child. ARNOLD GESELL, FRANCES L. ILG, AND GLENNA E. BULLIS. Chapt. 15, 329. Hoeber, N. Y. $7.50.

When *Vision* appeared in 1949, its outstanding contribution was its firm repeated emphasis on the close, dependent relationship, from the fetal stage through early childhood, between visual growth and the motor activity of the body. This still seems, after more than three years, to be its particular mission.

Gesell and his associates not only stress the dynamic relationship existing between what are termed "the total action system" and the "visual system," but they report thought-provoking experiments to demonstrate their thesis. Cinema records, supplemented by observational reports, have been used to good advantage. One of their research procedures, which should be repeated and extended, involved the use of the Copeland streak retinoscope to make a report of changes taking place in refraction which correlated with motor activity changes in the child. Records were obtained at seven age levels, from 30 weeks to four years. The findings for these children with normal vision suggest the possibility of an important contribution some day by ophthalmologists and neurologists to psychologists or educators faced with the problem of evaluating the visually atypical child who is thought to have additional basic disabilities.

The subjects of experiments reported in *Vision* are biologically and environmentally favored children. They do not represent a normal distribution of the child population. However, probably for the purposes of this book, the selection of subjects has been a fortunate one since it has made possible the establishment of "gradients" against which results obtained by other experimenters may be checked. Clinically speaking, when comparisons are to be made in terms of some particular child, it is important that the user of data from this book keep in mind the background of the group from whom the results were obtained.

A chapter reporting case histories of handicapped children provides something of a backdrop for what has come before. Not only are the histories of interest in themselves, but they point up the existence of growth potentials which are ready to function dynamically, if given a chance, even when one subsystem of the total action system is completely lacking, or when two or more are functionally hampered.

From the point of view of the scientifically minded specialist who is particularly interested in vision and in early childhood development, the value of the book is impaired by its strained and erudite vocabulary which constantly raises questions regarding meaning, and sometimes accuracy, of terminology. The value of the book is still further limited for this reviewer by the presence of certain classifications which must be intellectually accepted, temporarily at least, if one is to profit by much that is stimulating and valuable. For instance, even after a careful study

of a chart on page 165, which presents a Functional Complex of the Visual System, and after reading its accompanying chapter, the reviewer's mind still finds it hard to accept statements such as this, on page 286: "There are two major types of strabismus—one predominantly visceral, the other predominantly skeletal."

An important and profitable part of the book consists of the Appendices: *A.*—Examination Sequence and Procedures; *B.*—The Ontogenetic Gradients of Visual Behavior; *C.*—Selected References. The last takes the place of a bibliography and might, therefore, have been tied in more closely with the text by means of footnotes.—*Kathryn E. Maxfield, Ph.D.*

Headache and Other Head Pain. HAROLD G. WOLFF, New York, Oxford University Press.

In spite of its great frequency headache is usually considered as a symptom and its true nature and etiology have been little understood. Its occurrence and treatment have generally been reviewed under the description of the malfunction of some particular organ. In this excellent treatise, the consideration has been general and includes all specialties, not neglecting the psychosomatic factor. The author has acquired most of his knowledge relative to pain sensitivity by testing various tissues during operations upon the cranium and the intra-cranial structures. Thus it was learned that the tissues covering the cranium are all sensitive to pain, especially the arteries. Of the intracranial structures, the large veins and arteries and the brain surface are pain-sensitive. The cranium and brain parenchyma are insensitive.

Changes of intracranial pressure, both increased and decreased, cause headache. Its mechanism is described, as is the type of headache accompanying brain tumor. Distention of cerebral and pial arteries leads to head pain, as may be proved by injection of histamine. The headache accompanying fevers is produced by increased amplitude of the pulsation of arteries.

A special, and very valuable chapter is devoted to the consideration of the headache of migraine and its mechanism. Arterial hypertension head pains are not closely related to the blood pressure and are often relieved by pressure upon the temporal arteries.

Infection and inflammation of the paranasal sinuses are common causes of head pain, the characteristics of which are described for the various cavities. The head pains of dental disease and otologic pathology are well delineated. The most common cause of headache, that of ocular origin is fully considered and evaluated. Numerous other minor causes of headache or pain or reviewed.

Wolff's recent book on Headache and Other Head Pains is a most valuable addition to the library of every medical practitioner and definitely fills a need for the better understanding of this almost universal symptom which bedevils modern man.—*Eugene M. Blake.*

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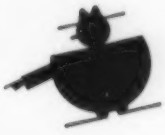

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1. Freed, S. C., Internat. Rec. Med. 166:465 (Nov.) 1953. 2. Rees, L., J. Ment. Sc. 99:62 (Jan.) 1953. 3. Morton, J. H., et al., Am. J. Obst. & Gynec. 65:1182 (June) 1953. 4. Morton, J. H., Internat. Rec. Med. 166:505 (Nov.) 1953.

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